

UNITED STATES PATENT
APPLICATION OF

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FOR

PEPTIDE INHIBITORS OF HEPATITIS C VIRUS NS3 PROTEASE

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TITLE

Peptide Inhibitors of Hepatitis C Virus NS3 Protease

FIELD OF THE INVENTION

10 The present invention relates generally to a novel
class of peptides, which are useful as serine protease
inhibitors, and more particularly as Hepatitis C virus
(HCV) NS3 protease inhibitors. This invention also relates
to pharmaceutical compositions comprising these compounds
and methods of using the same in the treatment of HCV
15 infection.

BACKGROUND OF THE INVENTION

Hepatitis C virus is the major cause of transfusion
and community-acquired non-A, non-B hepatitis worldwide.
Approximately 2% of the world's population are infected
20 with the virus. In the United States, hepatitis C
represents approximately 20% of cases of acute hepatitis.
Unfortunately, self-limited hepatitis is not the most
common course of acute HCV infection. In the majority of
patients, symptoms of acute hepatitis resolve, but alanine
25 aminotransferase (a liver enzyme diagnostic for liver
damage) levels often remain elevated and HCV RNA persists.
Indeed, a propensity to chronicity is the most
distinguishing characteristic of hepatitis C, occurring in
at least 85% of patients with acute HCV infection. The
30 factors that lead to chronicity in hepatitis C are not well
defined. Chronic HCV infection is associated with increased
incidence of liver cirrhosis and liver cancer. No vaccines
are available for this virus, and current treatment is
restricted to the use of alpha interferon, which is
35 effective in only 15-20% of patients. Recent clinical
studies have shown that combination therapy of alpha
interferon and ribavirin leads to sustained efficacy in 40%
of patients (Poynard, T. et al. *Lancet* (1998), 352, 1426-
1432.). However, a majority of patients still either fail

5 to respond or relapse after completion of therapy. Thus,
there is a clear need to develop more effective
therapeutics for treatment of HCV-associated hepatitis.

HCV is a positive-stranded RNA virus. Based on
comparison of deduced amino acid sequence and the extensive
10 similarity in the 5' untranslated region, HCV has been
classified as a separate genus in the Flaviviridae family,
which also includes flaviviruses such as yellow fever virus
and animal pestiviruses like bovine viral diarrhea virus
and swine fever virus. All members of the Flaviviridae
15 family have enveloped virions that contain a positive
stranded RNA genome encoding all known virus-specific
proteins via translation of a single, uninterrupted, open
reading frame.

Considerable heterogeneity is found within the
20 nucleotide and encoded amino acid sequence throughout the
HCV genome. At least six major genotypes have been
characterized, and more than 50 subtypes have been
described. The major genotypes of HCV differ in their
distribution worldwide, and the clinical significance of
25 the genetic heterogeneity of HCV remains elusive despite
numerous studies of the possible effect of genotypes on
pathogenesis and therapy.

The RNA genome is about 9.6 Kb in length, and encodes
a single polypeptide of about 3000 amino acids. The 5'
30 untranslated region contains an internal ribosome entry
site (IRES), which directs cellular ribosomes to the
correct AUG for initiation of translation. As was
determined by transient expression of cloned HCV cDNAs, the
precursor protein is cotranslationally and
35 posttranslationally processed into at least 10 viral
structural and nonstructural (NS) proteins by the action of
a host signal peptidase and by two distinct viral
proteinase activities. The translated product contains the
following proteins: core-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-
40 NS5B.

5 The N-terminal portion of NS3 functions as a
proteolytic enzyme that is responsible for the cleavage of
sites liberating the nonstructural proteins NS4A, NS4B,
NS5A, and NS5B. NS3 has further been shown to be a serine
protease. Although the functions of the NS proteins are
10 not completely defined, it is known that NS4A is a protease
cofactor and NS5B is an RNA polymerase involved in viral
replication. Thus, agents that inhibit NS3 proteolytic
processing of the viral polyprotein are expected to have
antiviral activity.

15 Extensive efforts toward the development of HCV NS3
protease inhibitors have resulted in the following
disclosures: WO 98/17679 (Tung et al.) describes a large
class of generic peptide and peptidomimetic inhibitors with
the following formula: $U-E^8-E^7-E^6-E^5-E^4-NH-CH(CH_2G^1)-W^1$,
20 wherein W^1 is a variety of electrophilic groups. E^4
represents either an amino acid or one of a series of
peptidomimetic groups. No example of compounds wherein W^1
is boronic acid or ester is disclosed or enabled in WO
98/17679. Additionally, compounds with extended aralkyl or
25 heteroaralkyl P_1 substituents as disclosed in the present
application are not disclosed, enabled or exemplified in WO
98/17679.

 WO 98/22496 (Attwood et al.) discloses solely
hexapeptide inhibitors of the following general formula:
30 $R^9-NH-CH(R^8)-CO-NH-CH(R^7)-CO-N(R^6)-CH(R^5)-CO-NH-CH(R^4)-CO-$
 $N(R^3)-CH(R^2)-CO-NH-CH(R^1)-E$ wherein E is either an aldehyde
or a boronic acid. Compounds with extended aralkyl or
heteroaralkyl P_1 substituents as disclosed in the present
application are not specifically disclosed, enabled or
35 exemplified in WO 98/22496.

 WO 99/07734 (Llinas-Brunet et al.) discloses tetra- to
hexa-peptide analogs containing a P_1 electrophilic carbonyl
group, a phosphonate ester, or an aza-aminoacid analog. WO
99/07733 (Llinas-Brunet et al.) describes related peptides
40 terminating in a carboxylate. Similar compounds are

5 reported by Steinkuhler et al. *Biochemistry* (1998), 37,
8899-8905 and Ingallinella et al. *Biochemistry* (1998), 37,
8906-8914. None of these publications teaches the making
and use of compounds with aralkyl or heteroaralkyl P1
substituents.

10 WO 99/50230 (Tung et al.) discloses peptidomimetics
containing a 5 or 6-membered carbocyclic ring at the P2
position. Tung et al. does not teach the aralkyl or
heteroaralkyl P1 substituents of the present invention.

WO 00/09543 (Llinas-Brunet et al.) discloses
15 tripeptides containing a substituted proline residue at P2
and an aminocyclopropanecarboxylate derivative at P1. A
related disclosure, WO 00/09558 (Llinas-Brunet et al.),
discloses tetra- to hexapeptides with the same P1 and P2
structure as WO 00/09543.

20 Other peptide inhibitors of HCV protease have been
disclosed. WO 98/46630 (Hart et al.) has described hepta-
peptide analogs containing an ester linkage at the scissile
bond. WO 97/43310 (Zhang et al.) discloses high molecular
weight peptide inhibitors. The present invention is
25 distinct from the compounds of WO 98/46630 or WO 97/43310.

Additionally, literature regarding HCV NS3 protease
inhibitors suggest that the S1 pocket of the NS3 protease
enzyme can only accommodate small aliphatic P1 residues.
(Pizzi et al. *Proc. Natl. Acad. Sci. USA* (1994), 91, 888-
30 892; Urbani et al. *J. Biol. Chem.* (1997) 272, 9204-9209;
Perni, Robert B. *Drug News Perspective* (2000), 13, 69-77).
Thus, the general literature regarding HCV NS3 protease
inhibitors does not suggest or provide the motivation to
one skilled in the art to make extended aralkyl P1
35 inhibitors of the present invention.

Based on the large number of persons currently
infected with HCV and the limited treatments available, it
is desirable to discover new inhibitors of HCV NS3
protease. The instant invention discloses a class of novel
40 peptides with extended P1 residues that exhibit inhibitory
activity against HCV NS3 protease. Further, the present

5 invention discloses unexpected benefit of HCV NS3 protease inhibitory selectivity over inhibition of elastase and/or chymotrypsin.

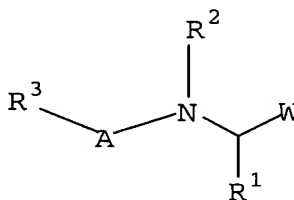
SUMMARY OF THE INVENTION

10 One object of the present invention is to provide compounds, or pharmaceutically acceptable salt forms or prodrugs thereof, which are useful as inhibitors of hepatitis C virus protease, more specifically, the NS3 protease.

15 It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt form or prodrug thereof.

20 It is another object of the present invention to provide a method for the treatment or prevention of HCV comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt form
25 or prodrug thereof.

These and other objects of the invention, which will become apparent during the following detailed description, have been achieved by the discovery that compounds of Formula (I):

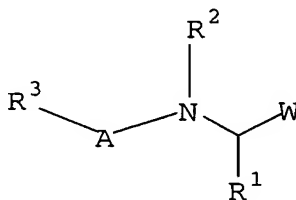


(I)

30 or pharmaceutically acceptable salt forms or prodrugs thereof, wherein R¹, R², R³, W, and A are defined below,
35 are effective inhibitors of HCV NS3 protease.

DETAILED DESCRIPTION OF THE INVENTION

[1] Thus, in one embodiment, the present invention provides a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt form or prodrug thereof, wherein:

W is selected from the group:

- B(Y¹)(Y²),
- C(=O)C(=O)-Q,
- C(=O)C(=O)NH-Q,
- C(=O)C(=O)-O-Q,
- C(=O)CF₂C(=O)NH-Q;
- C(=O)CF₃,
- C(=O)CF₂CF₃, and
- C(=O)H;

Y¹ and Y² are independently selected from:

- a) -OH,
- b) -F,
- c) -NR⁴R⁵,
- d) C₁-C₈ alkoxy, and

when taken together with B, Y¹ and Y² form:

- e) a cyclic boronic ester where said cyclic boronic ester contains from 2 to 20 carbon atoms, and, optionally, 1, 2, or 3 heteroatoms which can be N, S, or O;

- 5 f) a cyclic boronic amide where said cyclic boronic
amide contains from 2 to 20 carbon atoms and,
optionally, 1, 2, or 3 heteroatoms which can be N,
S, or O; or
- 10 g) a cyclic boronic amide-ester where said cyclic
boronic amide-ester contains from 2 to 20 carbon
atoms and, optionally, 1, 2, or 3 heteroatoms which
can be N, S, or O;

Q is selected from $-(CR^6R^{6c})_p-Q^1$, $-(CR^6R^{6c})_p-Q^2$,
15 C_2-C_4 alkenyl substituted with Q^1 ,
 C_2-C_4 alkynyl substituted with Q^1 , and
an amino acid residue;

p is 1, 2, 3 or 4;

20 Q^1 is selected from the group:

$-CO_2R^7$, $-SO_2R^7$, $-SO_3R^7$, $-P(O)_2R^7$, $-P(O)_3R^7$,

aryl substituted with 0-4 Q^{1a} , and

25 5-6 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; and said 5-6 membered
heterocyclic ring system is substituted with 0-4
 Q^{1a} ;

30 Q^{1a} is H, F, Cl, Br, I, $-NO_2$, $-CN$, $-NCS$, $-CF_3$, $-OCF_3$,
 $-CO_2R^8$, $-C(=O)NR^8R^9$, $-NHC(=O)R^8$, $-SO_2R^8$, $-SO_2NR^8R^9$,
 $-NR^8R^9$, $-OR^8$, $-SR^8$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or
 C_1-C_4 haloalkoxy;

35 Q^2 is $-X^1-NR^{10}-Z$, $-NR^{10}-X^2-Z$, or $-X^1-NR^{10}-X^2-Z$;

X^1 and X^2 are independently selected from: $-C(=O)-$, $-S-$,
 $-S(=O)-$, $-S(=O)_2-$, $-P(O)-$, $-P(O)_2-$, and $-P(O)_3-$;

5

Z is C₁-C₄ haloalkyl,

C₁-C₄ alkyl substituted with 0-3 Z^a,

C₂-C₄ alkenyl substituted with 0-3 Z^a,

C₂-C₄ alkynyl substituted with 0-3 Z^a,

10 C₃-C₁₀ cycloalkyl substituted with 0-5 Z^b,

C₃-C₁₀ carbocycle substituted with 0-5 Z^b,

6-10 membered aryl substituted with 0-5 Z^b, or

15 5-10 membered heterocyclic ring system consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N; optionally saturated, partially unsaturated or unsaturated; and said 5-10 membered heterocyclic ring system is substituted with 0-4 Z^b;

20 Z^a is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,

-CO₂R⁸, -C(=O)NR⁸R⁹, -NHC(=O)R⁸, -NR⁸R⁹, -OR⁸, -SR⁸,

-S(=O)R⁸, -SO₂R⁸, -SO₂NR⁸R⁹, C₁-C₄ alkyl,

C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy,

C₃-C₇ cycloalkyl substituted with 0-5 Z^b,

25 C₃-C₁₀ carbocycle substituted with 0-5 Z^b,

6-10 membered aryl substituted with 0-5 Z^b, or

5-10 membered heterocyclic ring system consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N; optionally saturated, partially unsaturated or unsaturated; and said 5-10 membered heterocyclic ring system is substituted with 0-4 Z^b;

Z^b is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,

35 -CO₂R⁸, -C(=O)NR⁸R⁹, -NHC(=O)R⁸, -NR⁸R⁹, -OR⁸, -SR⁸,

-S(=O)R⁸, -SO₂R⁸, -SO₂NR⁸R⁹, C₁-C₄ alkyl, C₁-C₄

haloalkyl, C₁-C₄ haloalkoxy,

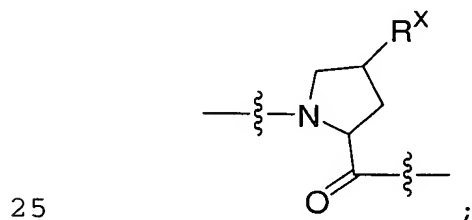
C₃-C₇ cycloalkyl substituted with 0-5 Z^c,

5 C₃-C₁₀ carbocycle substituted with 0-5 Z^c,
 6-10 membered aryl substituted with 0-5 Z^c, or
 5-10 membered heterocyclic ring system consisting of
 carbon atoms and 1-4 heteroatoms selected from the
 group: O, S, and N; optionally saturated, partially
 10 unsaturated or unsaturated; and said 5-10 membered
 heterocyclic ring system is substituted with 0-4
 Z^c;

Z^c is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃, -CO₂R⁸,
 15 -C(=O)NR⁸R⁹, -NHC(=O)R⁸, -NR⁸R⁹, -OR⁸, -SR⁸, -S(=O)R⁸,
 -SO₂R⁸, -SO₂NR⁸R⁹, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or
 C₁-C₄ haloalkoxy;

A is A²-A³, A²-A³-A⁴, A²-A³-A⁴-A⁵, A²-A³-A⁴-A⁵-A⁶, or
 20 A²-A³-A⁴-A⁵-A⁶-A⁷;

A² is a natural amino acid, a modified amino acid, an
 unnatural amino acid, or



wherein said amino acid is of either D or L configuration;

R^X is H, F, Cl, Br, I, -CF₃, -OCF₃, -(CH₂)_m-R¹⁶-(CH₂)_n-R¹²,
 30 or -CO₂R¹²;

m and n are independently selected from 0, 1, 2, and 3;

A³, A⁴, A⁵, A⁶, and A⁷ are independently selected from an
 35 amino acid residue; wherein said amino acid residue,
 at each occurrence, is independently selected from a

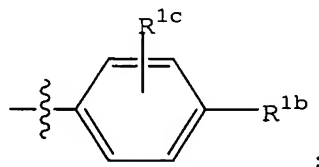
10

5 natural amino acid, a modified amino acid, or an unnatural amino acid; wherein said natural, modified or unnatural amino acid is of either D or L configuration;

10 R^1 is $-\text{CH}_2\text{CH}_2-\text{R}^{1a}$, $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{R}^{1a}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{R}^{1a}$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{R}^{1a}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{R}^{1a}$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_2\text{CH}_3)_2$, or
 $-\text{CH}_2\text{CH}_2\text{CH}_2$ -cyclobutyl;

15

R^{1a} is



R^{1b} is selected at each occurrence from the group:

20 H, C_1 - C_4 alkyl, F, Cl, Br, I, -OH, C_1 - C_4 alkoxy, phenoxy, benzyloxy, -SH, -CN, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{OR}^{1d}$,
 $-\text{NR}^{1d}\text{R}^{1d}$, $-\text{CF}_3$, $-\text{OCF}_3$, C_3 - C_6 cycloalkyl, and aryl substituted by 0-3 R^{1c} ;

25 R^{1c} is selected at each occurrence from the group:

methyl, ethyl, Cl, F, Br, I, OH, methoxy, ethoxy, -CN, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{OR}^{1d}$, $\text{NR}^{1d}\text{R}^{1d}$, $-\text{CF}_3$, and $-\text{OCF}_3$;

R^{1d} is H, C_1 - C_4 alkyl, phenyl or benzyl;

30

R^2 is H, C_1 - C_4 alkyl, aryl, aryl(C_1 - C_4 alkyl)-, or C_3 - C_6 cycloalkyl;

R^3 is H, C_1 - C_4 alkyl, aryl, aryl(C_1 - C_4 alkyl)-, $-\text{C}(=\text{O})\text{R}^{11}$,
 35 $-\text{CO}_2\text{R}^{11}$, $-\text{C}(=\text{O})\text{NHR}^{11}$, $-\text{S}(=\text{O})\text{R}^{11}$, $-\text{S}(=\text{O})_2\text{R}^{11}$, or an NH_2 -blocking group;

5

R⁴ and R⁵, are independently selected from: H, C₁-C₄ alkyl, aryl(C₁-C₄ alkyl)-, and C₃-C₇ cycloalkyl;

10

R⁶ is selected from the group: H, -CO₂R⁷, -NR⁷R⁷, and C₁-C₆ alkyl substituted with 0-1 R^{6a};

15

R^{6a} is selected from the group: halo, -NO₂, -CN, -CF₃, -CO₂R⁷, -NR⁷R⁷, -OR⁷, -SR⁷, -C(=NH)NH₂, and aryl substituted with 0-1 R^{6b};

R^{6b} is selected from the group: -CO₂H, -NH₂, -OH, -SH, and -C(=NH)NH₂;

20

R^{6c} is H or C₁-C₄ alkyl;

25

R⁷ at each occurrence is independently selected from the group: H, C₁-C₄ alkyl, aryl, and aryl(C₁-C₄ alkyl)-, wherein aryl is optionally substituted with 0-3 substituents selected from -CH₃, -NO₂, -CN, -OH, -OCH₃, -SO₂CH₃, -CF₃, Cl, Br, I, and F;

30

alternatively, -NR⁷R⁷ may optionally form a 5-6 membered heterocycle consisting of carbon atoms, a nitrogen atom, and optionally a second heteroatom selected from the group: O, S, and N;

R⁸ and R⁹ are independently selected from H, C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, and C₃-C₇ cycloalkyl;

35

alternatively, NR⁸R⁹ may form a 5-6 membered heterocycle consisting of carbon atoms, a nitrogen atom, and optionally a second heteroatom selected from the group: O, S, and N;

12

- 5 R^{10} is selected from the group: H,
 C_1 - C_4 alkyl substituted with 0-3 R^{13} ,
 C_3 - C_{10} carbocycle substituted with 0-3 R^{13} ,
 6-10 membered aryl substituted with 0-3 R^{13} , and
10 5-10 membered heterocyclic ring system consisting of
 carbon atoms and 1-4 heteroatoms selected from the
 group: O, S, and N; optionally saturated, partially
 unsaturated or unsaturated; said 5-10 membered
 heterocyclic ring system is substituted with 0-3
 R^{13} ;
- 15 R^{11} is C_1 - C_4 alkyl substituted with 0-1 R^{11a} ,
 6-10 membered aryl substituted with 0-2 R^{11b} , or
 5-10 membered heterocyclic ring system consisting of
 carbon atoms and 1-4 heteroatoms selected from the
20 group: O, S, and N; optionally saturated, partially
 unsaturated or unsaturated; said 5-10 membered
 heterocyclic ring system is substituted with 0-2
 R^{11b} ;
- 25 R^{11a} is C_1 - C_4 alkyl, halogen, $-OR^{14}$, $-SR^{14}$, $-NR^{14}R^{15}$, aryl,
 or a 5-6 membered heterocyclic ring system containing
 1, 2 or 3 heteroatoms selected from nitrogen, oxygen
 and sulfur;
- 30 R^{11b} is $-NO_2$, $-NH_2$, $-SO_3H$, $-SO_2CH_3$, $-CO_2H$, $-CF_3$, $-OH$, $-SH$,
 $-OCF_3$, Cl, Br, I, F, $=O$, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 -
 C_4 thioalkoxy, aryl, or aryl(C_1 - C_4 alkyl)-, wherein
 aryl is optionally substituted with 0-3 substituents
 selected from $-CH_3$, $-NO_2$, $-CN$, $-OH$, $-OCH_3$, $-SO_2CH_3$,
35 $-CF_3$, Cl, Br, I, and F;
- R^{12} is selected from the group: H;
 C_1 - C_6 alkyl substituted with 0-3 R^{12a} ;
 C_2 - C_6 alkenyl substituted with 0-3 R^{12a} ;

5 C₂-C₆ alkynyl substituted with 0-3 R^{12a};
C₃-C₇ cycloalkyl substituted with 0-3 R^{12a};
C₄-C₁₀ (cycloalkyl-alkyl) substituted with 0-3 R^{12a};
6-10 membered aryl substituted with 0-3 R^{12a}; and
5-10 membered heterocyclic ring system consisting of
10 carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
heterocyclic ring system is substituted with 0-2
R^{12a};

15

R^{12a} is independently selected from the group: C₁-C₆ alkoxy;
lower thioalkyl; sulfonyl; -NO₂; halogen; haloalkyl;
carboxyl; carboxy(lower alkyl); -OR¹⁴; -SR¹⁴; -NR¹⁴R¹⁵;
-C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵; -S(=O)₂R¹⁴;

20

C₁-C₆ alkyl substituted with 0-3 R^{12b};
C₂-C₆ alkenyl substituted with 0-3 R^{12b};
C₂-C₆ alkynyl substituted with 0-3 R^{12b};
C₃-C₇ cycloalkyl substituted with 0-3 R^{12b};
C₄-C₁₀ (alkylcycloalkyl) substituted with 0-3 R^{12b};

25

6-10 membered aryl substituted with 0-3 R^{12b}; and
5-10 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
30 heterocyclic ring system is substituted with 0-2
R^{12b};

R^{12b} is independently selected from the group: C₁-C₆ alkyl;
C₃-C₇ cycloalkyl; C₁-C₆ alkoxy; halogen; -OR¹⁴; -SR¹⁴;
35 -NR¹⁴R¹⁵; -C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵; -S(=O)₂R¹⁴;
-NO₂; haloalkyl; carboxyl; carboxy(lower alkyl); aryl;
and 5-10 membered heterocyclic ring system consisting

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5 of carbon atoms and 1-4 heteroatoms selected from
the group: O, S, and N; optionally saturated,
partially unsaturated or unsaturated; said 5-10
membered heterocyclic ring system is substituted
with C₁-C₆ alkyl;

10

R¹³ at each occurrence is independently selected from the
group: H, -NO₂, -SO₂OH, -SO₂CH₃, -CF₃, Cl, Br, I, F,
-NH₂, -NH(CH₃), -N(CH₃)₂, -NH(CH₂CH₃), -N(CH₂CH₃)₂, and
C₁-C₄ alkyl;

15

R¹⁴ and R¹⁵ are independently selected from the group: H,
C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, and C₃-C₇
cycloalkyl;

20 R¹⁶ is a bond, -O-, -S- or -NR¹⁷-; and

R¹⁷ is H, C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, or
C₃-C₆ cycloalkyl.

25 [2] In another embodiment, the present invention provides
a compound of Formula (I) or a pharmaceutically acceptable
salt or prodrug thereof, wherein:

W is -B(Y¹)(Y²) or -C(=O)C(=O)NH-Q;

30

Y¹ and Y² are independently selected from:

- a) -OH,
- b) -F,
- c) -NR⁴R⁵,

35

- d) C₁-C₈ alkoxy, and

when taken together with B, Y¹ and Y² form:

- e) a cyclic boronic ester where said cyclic boronic
ester contains from 2 to 20 carbon atoms, and,
optionally, 1, 2, or 3 heteroatoms which can be N,
S, or O;

40

5

Q is selected from $-(CR^6R^{6c})_p-Q^1$,
 C_2-C_4 alkenyl substituted with Q^1 ,
 C_2-C_4 alkynyl substituted with Q^1 , and
 an amino acid residue;

10

p is 1, 2 or 3;

Q^1 is selected from the group:

$-CO_2R^7$, $-SO_2R^7$, $-SO_3R^7$,

15

aryl substituted with 0-4 Q^{1a} , and

5-6 membered heterocyclic ring system consisting of
 carbon atoms and 1-4 heteroatoms selected from the
 group: O, S, and N; optionally saturated, partially
 unsaturated or unsaturated; and said 5-6 membered
 heterocyclic ring system is substituted with 0-4
 Q^{1a} ;

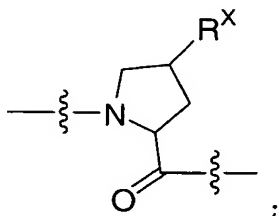
20

Q^{1a} is H, F, Cl, Br, I, $-NO_2$, $-CN$, $-NCS$, $-CF_3$, $-OCF_3$,
 $-CO_2R^8$, $-C(=O)NR^8R^9$, $-NHC(=O)R^8$, $-SO_2R^8$, $-SO_2NR^8R^9$,
 $-NR^8R^9$, $-OR^8$, $-SR^8$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or
 C_1-C_4 haloalkoxy;

25

A is A^2-A^3 , $A^2-A^3-A^4$, $A^2-A^3-A^4-A^5$, or $A^2-A^3-A^4-A^5-A^6$;

30 A^2 is a natural amino acid, a modified amino acid, an
 unnatural amino acid, or



35 wherein said amino acid is of either D or L configuration;

5

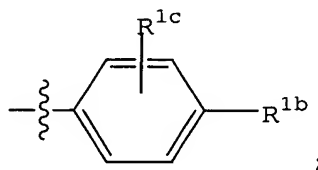
R^X is H or $-(CH_2)_m-R^{16}-(CH_2)_n-R^{12}$;

m and n are independently selected from 0, 1, or 2;

10 A^3 , A^4 , A^5 , and A^6 are independently selected from an amino acid residue wherein said amino acid residue, at each occurrence, is independently selected from a natural amino acid, a modified amino acid, or an unnatural amino acid wherein said natural, modified or unnatural
15 amino acid is of either D or L configuration;

R^1 is $-CH_2CH_2-R^{1a}$, $-CH_2CH_2CH_2-R^{1a}$, $-CH_2CH_2CH_2CH_2-R^{1a}$,
 $-CH_2CH_2CH_2CH_2CH_2-R^{1a}$, $-CH_2CH_2CH_2CH_2CH_2CH_2-R^{1a}$,
 $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$,
 20 $-CH_2CH_2CH_2C(CH_3)_2$, $-CH_2CH_2CH_2C(CH_2CH_3)_2$, or
 $-CH_2CH_2CH_2$ -cyclobutyl;

R^{1a} is



25

R^{1b} is selected at each occurrence from the group:
 H, C_1 - C_4 alkyl, F, Cl, Br, I, -OH, C_1 - C_4 alkoxy,
 phenoxy, benzyloxy, -SH, -CN, -NO₂, $-C(=O)OR^{1d}$,
 $-NR^{1d}R^{1d}$, -CF₃, -OCF₃, C_3 - C_6 cycloalkyl, and aryl
 30 substituted by 0-3 R^{1c} ;

R^{1c} is selected at each occurrence from the group:
 methyl, ethyl, Cl, F, Br, I, OH, methoxy, ethoxy, -CN,
 $-NO_2$, $-C(=O)OR^{1d}$, $NR^{1d}R^{1d}$, -CF₃, and -OCF₃;

35

R^{1d} is H, C_1 - C_4 alkyl, phenyl or benzyl;

5

R² is H, C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, or
C₃-C₆ cycloalkyl;

10

R³ is H, C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, -C(=O)R¹¹,
-CO₂R¹¹, -C(=O)NHR¹¹, -S(=O)R¹¹, -S(=O)₂R¹¹, or
an NH₂-blocking group;

15

R⁴ and R⁵, are independently selected from: H, C₁-C₄ alkyl,
aryl(C₁-C₄ alkyl)-, and C₃-C₇ cycloalkyl;

R⁶ is selected from the group: H, -CO₂R⁷, -NR⁷R⁷, and C₁-C₆
alkyl substituted with 0-1 R^{6a};

20

R^{6a} is selected from the group: halo, -NO₂, -CN, -CF₃,
-CO₂R⁷, -NR⁷R⁷, -OR⁷, -SR⁷, -C(=NH)NH₂, and aryl
substituted with 0-1 R^{6b};

25

R^{6b} is selected from the group: -CO₂H, -NH₂, -OH, -SH, and
-C(=NH)NH₂;

R^{6c} is H or C₁-C₄ alkyl;

30

R⁷ at each occurrence is independently selected from the
group: H, C₁-C₄ alkyl, aryl, and aryl(C₁-C₄ alkyl)-,
wherein aryl is optionally substituted with 0-3
substituents selected from -CH₃, -NO₂, -CN, -OH,
-OCH₃, -SO₂CH₃, -CF₃, Cl, Br, I, and F;

35

alternatively, -NR⁷R⁷ may optionally form a 5-6 membered
heterocycle consisting of carbon atoms, a nitrogen
atom, and optionally a second heteroatom selected from
the group: O, S, and N;

5 R⁸ and R⁹ are independently selected from H, C₁-C₄ alkyl, aryl(C₁-C₄ alkyl)-, and C₃-C₇ cycloalkyl;

alternatively, NR⁸R⁹ may form a 5-6 membered heterocycle consisting of carbon atoms, a nitrogen atom, and
10 optionally a second heteroatom selected from the group: O, S, and N;

R¹¹ is C₁-C₄ alkyl substituted with 0-1 R^{11a},
6-10 membered aryl substituted with 0-2 R^{11b}, or
15 5-10 membered heterocyclic ring system consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N; optionally saturated, partially unsaturated or unsaturated; said 5-10 membered heterocyclic ring system is substituted with 0-2
20 R^{11b};

R^{11a} is C₁-C₄ alkyl, halogen, -OR¹⁴, -SR¹⁴, -NR¹⁴R¹⁵, aryl, or a 5-6 membered heterocyclic ring system containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen
25 and sulfur;

R^{11b} is -NO₂, -NH₂, -SO₃H, -SO₂CH₃, -CO₂H, -CF₃, -OH, -SH, -OCF₃, Cl, Br, I, F, =O, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, aryl, or aryl(C₁-C₄ alkyl)-, wherein
30 aryl is optionally substituted with 0-3 substituents selected from -CH₃, -NO₂, -CN, -OH, -OCH₃, -SO₂CH₃, -CF₃, Cl, Br, I, and F;

R¹² is selected from the group: H;
35 C₁-C₆ alkyl substituted with 0-3 R^{12a};
C₂-C₆ alkenyl substituted with 0-3 R^{12a};
C₂-C₆ alkynyl substituted with 0-3 R^{12a};
C₃-C₇ cycloalkyl substituted with 0-3 R^{12a};
C₄-C₁₀ (cycloalkyl-alkyl) substituted with 0-3 R^{12a};

5 6-10 membered aryl substituted with 0-3 R^{12a}; and
5-10 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
10 heterocyclic ring system is substituted with 0-2
R^{12a};

R^{12a} is independently selected from the group: C₁-C₆ alkoxy;
lower thioalkyl; sulfonyl; -NO₂; halogen; haloalkyl;
15 carboxyl; carboxy(lower alkyl); -OR¹⁴; -SR¹⁴; -NR¹⁴R¹⁵;
-C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵; -S(=O)₂R¹⁴;
C₁-C₆ alkyl substituted with 0-3 R^{12b};
C₂-C₆ alkenyl substituted with 0-3 R^{12b};
C₂-C₆ alkynyl substituted with 0-3 R^{12b};
20 C₃-C₇ cycloalkyl substituted with 0-3 R^{12b};
C₄-C₁₀ (alkylcycloalkyl) substituted with 0-3 R^{12b};
6-10 membered aryl substituted with 0-3 R^{12b}; and
5-10 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
25 group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
heterocyclic ring system is substituted with 0-2
R^{12b};

30 R^{12b} is independently selected from the group: C₁-C₆ alkyl;
C₃-C₇ cycloalkyl; C₁-C₆ alkoxy; halogen; -OR¹⁴; -SR¹⁴;
-NR¹⁴R¹⁵; -C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵; -S(=O)₂R¹⁴;
-NO₂; haloalkyl; carboxyl; carboxy(lower alkyl); aryl;
and 5-10 membered heterocyclic ring system consisting
35 of carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
heterocyclic ring system is substituted with C₁-C₆
alkyl;

5

R¹⁴ and R¹⁵ are independently selected from the group: H, C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, and C₃-C₇ cycloalkyl;

R¹⁶ is a bond, -O-, -S- or -NR¹⁷-; and

10

R¹⁷ is H, C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, or C₃-C₆ cycloalkyl.

[3] In an alternative embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein:

15

W is -B(Y¹)(Y²);

20 Y¹ and Y² are independently selected from:

- a) -OH,
- b) -F,
- c) C₁-C₈ alkoxy, and

when taken together with B, Y¹ and Y² form:

25

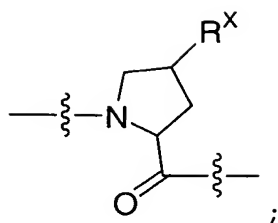
- d) a cyclic boronic ester where said cyclic boronic ester contains from 2 to 16 carbon atoms, and, optionally, 1, 2, or 3 heteroatoms which can be N, S, or O;

30 A is A²-A³, A²-A³-A⁴, A²-A³-A⁴-A⁵, or A²-A³-A⁴-A⁵-A⁶;

A² is Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr, Trp, Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa, Gla, Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl), cyclohexylglycine, cyclohexylalanine, cyclopropylglycine, t-butylglycine, phenylglycine, 3,3-diphenylalanine, or

40

5



10 A^3 , A^4 , A^5 , and A^6 are independently selected from an amino acid residue wherein said amino acid residue, at each occurrence, is independently selected from the group:
 Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr, Trp, Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa, Gla, Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe), Glu(OMe),
 15 Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl), cyclohexylglycine, cyclohexylalanine, cyclopropylglycine, t-butylglycine, phenylglycine, and 3,3-diphenylalanine;

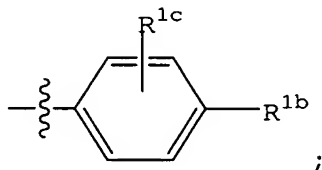
20

R^X is H or $-(CH_2)_m-R^{16}-(CH_2)_n-R^{12}$;

m and n are independently selected from 0, 1, or 2;

25 R^1 is $-CH_2CH_2-R^{1a}$, $-CH_2CH_2CH_2CH_2-R^{1a}$, or $-CH_2CH_2CH_2CH_2CH_2-R^{1a}$.

R^{1a} is



30 R^{1b} is selected at each occurrence from the group:
 H, C_1 - C_4 alkyl, F, Cl, Br, I, -OH, C_1 - C_4 alkoxy, phenoxy, benzyloxy, -SH, -CN, -NO₂, -C(=O)OR^{1d},

5 -NR^{1d}R^{1d}, -CF₃, -OCF₃, C₃-C₆ cycloalkyl, and aryl
substituted by 0-3 R^{1c};

R^{1c} is selected at each occurrence from the group: methyl,
ethyl, Cl, F, Br, I, OH, methoxy, ethoxy, -CN, -NO₂,
10 -C(=O)OR^{1d}, NR^{1d}R^{1d}, -CF₃, and -OCF₃;

R^{1d} is H, C₁-C₄ alkyl, phenyl or benzyl;

R² is H, C₁-C₄ alkyl, phenyl or benzyl;
15

R³ is H, C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, -C(=O)R¹¹,
-CO₂R¹¹, -C(=O)NHR¹¹, or an NH₂-blocking group;

R¹¹ is C₁-C₄ alkyl substituted with 0-1 R^{11a},
20 6-10 membered aryl substituted with 0-2 R^{11b}, or
5-10 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
25 heterocyclic ring system is substituted with 0-2
R^{11b};

R^{11a} is C₁-C₄ alkyl, halogen, -OR¹⁴, -SR¹⁴, -NR¹⁴R¹⁵, aryl,
or a 5-6 membered heterocyclic ring system containing
30 1, 2 or 3 heteroatoms selected from nitrogen, oxygen
and sulfur;

R^{11b} is -NO₂, -NH₂, -SO₃H, -SO₂CH₃, -CO₂H, -CF₃, -OH, -SH,
-OCF₃, Cl, Br, I, F, =O, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-
35 C₄ thioalkoxy, aryl, or aryl(C₁-C₄ alkyl)-, wherein
aryl is optionally substituted with 0-3 substituents
selected from -CH₃, -NO₂, -CN, -OH, -OCH₃, -SO₂CH₃,
-CF₃, Cl, Br, I, and F;

5 R¹² is selected from the group: H;

C₁-C₆ alkyl substituted with 0-3 R^{12a};

C₂-C₆ alkenyl substituted with 0-3 R^{12a};

C₂-C₆ alkynyl substituted with 0-3 R^{12a};

C₃-C₇ cycloalkyl substituted with 0-3 R^{12a};

10 C₄-C₁₀ (cycloalkyl-alkyl) substituted with 0-3 R^{12a};

6-10 membered aryl substituted with 0-3 R^{12a}; and

5-10 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
15 unsaturated or unsaturated; said 5-10 membered
heterocyclic ring system is substituted with 0-2
R^{12a};

R^{12a} is independently selected from the group: C₁-C₆ alkoxy;

20 lower thioalkyl; sulfonyl; -NO₂; halogen; haloalkyl;
carboxyl; carboxy(lower alkyl); -OR¹⁴; -SR¹⁴; -NR¹⁴R¹⁵;
-C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵; -S(=O)₂R¹⁴;

C₁-C₆ alkyl substituted with 0-3 R^{12b};

C₂-C₆ alkenyl substituted with 0-3 R^{12b};

25 C₂-C₆ alkynyl substituted with 0-3 R^{12b};

C₃-C₇ cycloalkyl substituted with 0-3 R^{12b};

C₄-C₁₀ (alkylcycloalkyl) substituted with 0-3 R^{12b};

6-10 membered aryl substituted with 0-3 R^{12b}; and

5-10 membered heterocyclic ring system consisting of
30 carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
heterocyclic ring system is substituted with 0-2
R^{12b};

35

R^{12b} is independently selected from the group: C₁-C₆ alkyl;

C₃-C₇ cycloalkyl; C₁-C₆ alkoxy; halogen; -OR¹⁴; -SR¹⁴;

-NR¹⁴R¹⁵; -C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵; -S(=O)₂R¹⁴;

5 -NO₂; haloalkyl; carboxyl; carboxy(lower alkyl); and
5-10 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
10 heterocyclic ring system is substituted with C₁-C₆
alkyl;

R¹⁴ and R¹⁵ are independently selected from the group: H,
C₁-C₄ alkyl, aryl, aryl(C₁-C₄ alkyl)-, and C₃-C₇
15 cycloalkyl;

R¹⁶ is a bond, -O-, -S- or -NR¹⁷-; and

R¹⁷ is H, C₁-C₄ alkyl, aryl or aryl(C₁-C₄ alkyl).
20

[4] In another alternative embodiment, the present
invention provides a compound of Formula (I) or a
pharmaceutically acceptable salt or prodrug thereof,
wherein:

25 W is -B(Y¹)(Y²);

Y¹ and Y² are independently selected from:

- a) -OH,
- b) C₁-C₆ alkoxy, or

30 when taken together with B, Y¹ and Y² form:

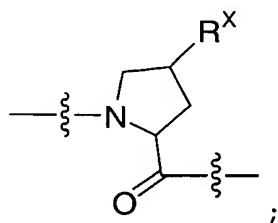
- d) a cyclic boronic ester where said cyclic boronic
ester contains from 2 to 16 carbon atoms;

A is A²-A³-A⁴, A²-A³-A⁴-A⁵, or A²-A³-A⁴-A⁵-A⁶;
35

A² is Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His,
Hyp, Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr,
Trp, Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa,
Gla, Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe),
40 Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu),

5 Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl),
cyclohexylglycine, cyclohexylalanine,
cyclopropylglycine, t-butylglycine, phenylglycine,
3,3-diphenylalanine, or

10



15

20

A³, A⁴, A⁵, and A⁶ are independently selected from an amino acid residue wherein said amino acid residue, at each occurrence, is independently selected from the group:
Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr, Trp, Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa, Gla, Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl), cyclohexylglycine, cyclohexylalanine, cyclopropylglycine, t-butylglycine, phenylglycine, and 3,3-diphenylalanine;

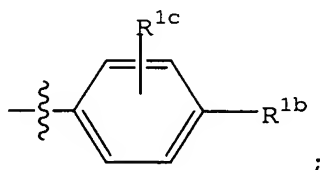
25 R^X is H or -(CH₂)_m-R¹⁶-(CH₂)_n-R¹²;

m and n are independently selected from 0, 1, or 2;

R¹ is -CH₂CH₂-R^{1a}, -CH₂CH₂CH₂CH₂-R^{1a}, or -CH₂CH₂CH₂CH₂CH₂-R^{1a}.

30

R^{1a} is



5 R^{1b} is selected at each occurrence from the group:
H, C_1 - C_4 alkyl, F, Cl, Br, I, -OH, C_1 - C_4 alkoxy,
phenoxy, benzyloxy, -SH, -CN, -NO₂, -C(=O)OR^{1d},
-NR^{1d}R^{1d}, -CF₃, -OCF₃, C_3 - C_6 cycloalkyl, and aryl
substituted by 0-3 R^{1c} ;

10

R^{1c} is selected at each occurrence from the group: methyl,
ethyl, Cl, F, Br, I, OH, methoxy, ethoxy, -CN, -NO₂,
-C(=O)OR^{1d}, NR^{1d}R^{1d}, -CF₃, and -OCF₃;

15 R^{1d} is H, C_1 - C_4 alkyl, phenyl or benzyl;

R^2 is H, methyl, ethyl, propyl, or butyl;

R^3 is H, C_1 - C_4 alkyl, aryl, aryl(C_1 - C_4 alkyl)-, -C(=O)R¹¹,
20 -CO₂R¹¹, -C(=O)NHR¹¹ or acetyl;

R^{11} is C_1 - C_4 alkyl substituted with 0-1 R^{11a} ,
phenyl substituted with 0-2 R^{11b} , or
5-6 membered heterocyclic ring system consisting of
25 carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-6 membered
heterocyclic ring system is substituted with 0-2
 R^{11b} ;

30

R^{11a} is C_1 - C_4 alkyl, halogen, -OR¹⁴, -SR¹⁴, -NR¹⁴R¹⁵, phenyl,
or a 5-6 membered heterocyclic ring system containing
1, 2 or 3 heteroatoms selected from nitrogen, oxygen
and sulfur;

35

R^{11b} is -NO₂, -NH₂, -SO₃H, -SO₂CH₃, -CO₂H, -CF₃, -OH, -SH,
-OCF₃, Cl, Br, I, F, =O, methyl, ethyl, propyl, butyl,
-OCH₃, -OCH₂CH₃, -SCH₃, -SCH₂CH₃, phenyl, or benzyl;

- 5 R^{12} is selected from the group: H;
 C_1 - C_4 alkyl substituted with 0-2 R^{12a} ;
 6-10 membered substituted with 0-3 R^{12a} ; and
 5-10 membered heterocyclic ring system consisting of
 carbon atoms and 1-4 heteroatoms selected from the
10 group: O, S, and N; optionally saturated, partially
 unsaturated or unsaturated; said 5-10 membered
 heterocyclic ring system is substituted with 0-2
 R^{12a} ;
- 15 R^{12a} is independently selected from the group: $-NO_2$;
 halogen; haloalkyl; carboxyl; carboxy(lower alkyl);
 $-OR^{14}$; $-SR^{14}$; $-NR^{14}R^{15}$; $-C(=O)NR^{14}R^{15}$; $-NR^{14}C(=O)R^{15}$;
 C_1 - C_4 alkyl substituted with 0-2 R^{12b} ;
 phenyl substituted with 0-3 R^{12b} ; and
20 5-6 membered heterocyclic ring system consisting of
 carbon atoms and 1-4 heteroatoms selected from the
 group: O, S, and N; optionally saturated, partially
 unsaturated or unsaturated; said 5-6 membered
 heterocyclic ring system is substituted with 0-2
25 R^{12b} ;
- R^{12b} is independently selected from the group: C_1 - C_4 alkyl;
 C_3 - C_6 cycloalkyl; F; Cl; Br; I; $-OR^{14}$; $-SR^{14}$;
 $-NR^{14}R^{15}$; $-C(=O)NR^{14}R^{15}$; $-NR^{14}C(=O)R^{15}$; $-S(=O)_2R^{14}$;
30 $-NO_2$; haloalkyl; carboxyl; carboxy(lower alkyl); and
 5-6 membered heterocyclic ring system consisting of
 carbon atoms and 1-4 heteroatoms selected from the
 group: O, S, and N; optionally saturated, partially
 unsaturated or unsaturated; said 5-6 membered
35 heterocyclic ring system is substituted with C_1 - C_6
 alkyl;
- R^{14} and R^{15} are independently selected from the group: H,
 C_1 - C_4 alkyl, phenyl and benzyl;

5

R^{16} is a bond, -O-, -S- or -NR¹⁷-; and

R^{17} is H, methyl, ethyl, propyl, butyl, phenyl or benzyl.

10 [5] In another alternative embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein:

15 W is -B(Y¹)(Y²);

Y¹ and Y² are independently selected from:

a) -OH,

b) C₁-C₆ alkoxy, or

20 when taken together with B, Y¹ and Y² form:

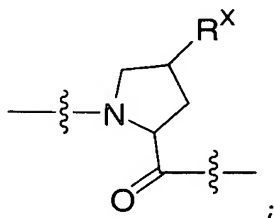
d) a cyclic boronic ester where said cyclic boronic ester contains from 2 to 14 carbon atoms;

A is A²-A³-A⁴, A²-A³-A⁴-A⁵, or A²-A³-A⁴-A⁵-A⁶;

25

A² is Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr, Trp, Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa, Gla, Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl), cyclohexylglycine, cyclohexylalanine, cyclopropylglycine, t-butylglycine, phenylglycine, 3,3-diphenylalanine, or

35



5

A³, A⁴, A⁵, and A⁶ are independently selected from an amino acid residue wherein said amino acid residue, at each occurrence, is independently selected from the group:

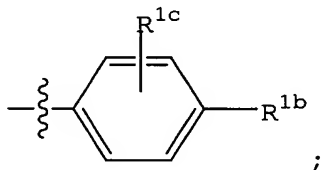
Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp,
 10 Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr, Trp,
 Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa, Gla,
 Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe), Glu(OMe),
 Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu),
 Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl),
 15 cyclohexylglycine, cyclohexylalanine,
 cyclopropylglycine, t-butylglycine, phenylglycine, and
 3,3-diphenylalanine;

R^x is H or -(CH₂)_m-R¹⁶-(CH₂)_n-R¹²;

20

m and n are independently selected from 0 or 1;

R¹ is -CH₂CH₂-R^{1a} or -CH₂CH₂CH₂CH₂-R^{1a};

25 R^{1a} is

R^{1b} is selected at each occurrence from the group:

H, C₁-C₄ alkyl, F, Cl, Br, I, -OH, C₁-C₄ alkoxy,
 30 phenoxy, benzyloxy, -SH, -CN, -NO₂, -C(=O)OR^{1d},
 -NR^{1d}R^{1d}, -CF₃, -OCF₃, C₃-C₆ cycloalkyl, and aryl
 substituted by 0-3 R^{1c};

R^{1c} is selected at each occurrence from the methyl, ethyl,
 35 Cl, F, Br, I, OH, methoxy, ethoxy, -CN, -NO₂,
 -C(=O)OR^{1d}, NR^{1d}R^{1d}, -CF₃, and -OCF₃;

5 R^{1d} is H, methyl, ethyl, propyl, butyl, phenyl or benzyl;

R² is H or methyl;

10 R³ is H, methyl, ethyl, propyl, butyl, phenyl, benzyl,
-C(=O)R¹¹, -CO₂R¹¹, -C(=O)NHR¹¹ or acetyl;

R¹¹ is C₁-C₄ alkyl substituted with 0-1 R^{11a},
phenyl substituted with 0-2 R^{11b}, or
15 5-6 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-6 membered
heterocyclic ring system is substituted with 0-2
R^{11b};

20 R^{11a} is methyl, ethyl propyl, butyl, F, Cl, Br, Cl, -OH,
-OCH₃, -SH, -SCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, phenyl, or a
5-6 membered heterocyclic ring system containing 1, 2
or 3 heteroatoms selected from nitrogen, oxygen and
25 sulfur;

R^{11b} is -NO₂, -NH₂, -SO₃H, -SO₂CH₃, -CO₂H, -CF₃, -OH, -SH,
-OCF₃, Cl, Br, I, F, =O, methyl, ethyl, propyl, butyl,
-OCH₃, -OCH₂CH₃, -SCH₃, -SCH₂CH₃, phenyl, or benzyl;

30

R¹² is selected from the group: H;

C₁-C₄ alkyl substituted with 0-2 R^{12a};
6-10 membered aryl substituted with 0-3 R^{12a}; and
5-10 membered heterocyclic ring system consisting of
35 carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
heterocyclic ring system is substituted with 0-2
R^{12a};

40

- 5 R^{12a} is independently selected from the group: $-NO_2$;
halogen; haloalkyl; carboxyl; carboxy(lower alkyl);
 $-OR^{14}$; $-SR^{14}$; $-NR^{14}R^{15}$; $-C(=O)NR^{14}R^{15}$; $-NR^{14}C(=O)R^{15}$;
 C_1 - C_4 alkyl substituted with 0-3 R^{12b} ;
phenyl substituted with 0-3 R^{12b} ; and
10 5-6 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated;
- 15 R^{12b} is independently selected from the group: C_1 - C_4 alkyl;
 C_3 - C_6 cycloalkyl; F; Cl; Br; I; $-OR^{14}$; $-SR^{14}$;
 $-NR^{14}R^{15}$; $-C(=O)NR^{14}R^{15}$; $-NR^{14}C(=O)R^{15}$; $-S(=O)_2R^{14}$;
 $-NO_2$; haloalkyl; carboxyl; carboxy(lower alkyl); and
5-6 membered heterocyclic ring system consisting of
20 carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated;

R^{14} and R^{15} are independently selected from the group: H,
25 methyl, ethyl, propyl, butyl, phenyl, and benzyl;

R^{16} is a bond, $-O-$, $-S-$ or $-NR^{17}-$; and

R^{17} is H, methyl, ethyl, propyl, butyl, phenyl, or benzyl.
30

[6] In another alternative embodiment, the present
invention provides a compound of Formula (I) or a
pharmaceutically acceptable salt or prodrug thereof,
wherein:

35 W is $-B(Y^1)(Y^2)$;

Y^1 and Y^2 are independently selected from:

- a) $-OH$,
40 b) C_1 - C_6 alkoxy, or

5 when taken together with B, Y¹ and Y² form:

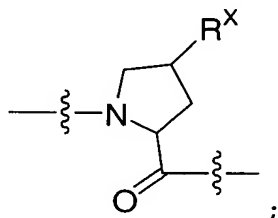
c) a cyclic boronic ester where said cyclic boronic ester is formed from the group: pinanediol, pinacol, 1,2-ethanediol, 1,3-propanediol, 1,2-propanediol, 2,3-butanediol, 1,2-
 10 diisopropylethanediol, 5,6-decanediol, 1,2-dicyclohexylethanediol, diethanolamine, and 1,2-diphenyl-1,2-ethanediol;

A is A²-A³-A⁴, A²-A³-A⁴-A⁵, or A²-A³-A⁴-A⁵-A⁶;

15

A² is Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr, Trp, Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa, Gla, Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe),
 20 Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl), cyclohexylglycine, cyclohexylalanine, cyclopropylglycine, t-butylglycine, phenylglycine, 3,3-diphenylalanine, or

25



A³, A⁴, A⁵, and A⁶ are independently selected from an amino acid residue wherein said amino acid residue, at each
 30 occurrence, is independently selected from the group:
 Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr, Trp, Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa, Gla, Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe), Glu(OMe),
 35 Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl),

5 cyclohexylglycine, cyclohexylalanine,
cyclopropylglycine, t-butylglycine, phenylglycine, and
3,3-diphenylalanine;

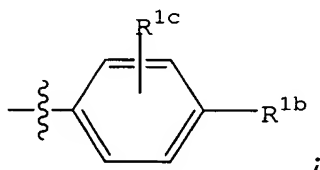
R^X is H, or $-(CH_2)_m-R^{16}-(CH_2)_n-R^{12}$;

10

m and n are independently selected from 0 or 1;

R^1 is $-CH_2CH_2-R^{1a}$ or $-CH_2CH_2CH_2CH_2-R^{1a}$;

15 R^{1a} is



R^{1b} is selected at each occurrence from the group:

20 H, C_1 - C_4 alkyl, F, Cl, Br, I, -OH, C_1 - C_4 alkoxy,
phenoxy, benzyloxy, -SH, -CN, -NO₂, -C(=O)OR^{1d},
-NR^{1d}R^{1d}, -CF₃, -OCF₃, C_3 - C_6 cycloalkyl, and aryl
substituted by 0-3 R^{1c} ;

25 R^{1c} is selected at each occurrence from the methyl, ethyl,
Cl, F, Br, I, OH, methoxy, ethoxy, -CN, -NO₂,
-C(=O)OR^{1d}, NR^{1d}R^{1d}, -CF₃, and -OCF₃;

R^{1d} is H, methyl, ethyl, propyl, butyl, phenyl or benzyl;

30 R^2 is H or methyl;

R^3 is H, methyl, ethyl, propyl, butyl, phenyl, benzyl,
-C(=O)R¹¹, -CO₂R¹¹, -C(=O)NHR¹¹ or acetyl;

35 R^{11} is C_1 - C_4 alkyl substituted with 0-1 R^{11a} ,
phenyl substituted with 0-2 R^{11b} , or

5 5-6 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-6 membered
heterocyclic ring system is substituted with 0-2
10 R^{11b};

R^{11a} is methyl, ethyl propyl, butyl, F, Cl, Br, Cl, -OH,
-OCH₃, -SH, -SCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, phenyl, or a
5-6 membered heterocyclic ring system containing 1, 2
15 or 3 heteroatoms selected from nitrogen, oxygen and
sulfur;

R^{11b} is -NO₂, -NH₂, -SO₃H, -SO₂CH₃, -CO₂H, -CF₃, -OH, -SH,
-OCF₃, Cl, Br, I, F, =O, methyl, ethyl, propyl, butyl,
20 -OCH₃, -OCH₂CH₃, -SCH₃, -SCH₂CH₃, phenyl, or benzyl;

R¹² is selected from the group: H;
C₁-C₄ alkyl substituted with 0-2 R^{12a};
6-10 member aryl substituted with 0-3 R^{12a}; and
25 5-10 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
heterocyclic ring system is substituted with 0-2
30 R^{12a};

R^{12a} is independently selected from the group: -NO₂;
halogen; haloalkyl; carboxyl; carboxy(lower alkyl);
-OR¹⁴; -SR¹⁴; -NR¹⁴R¹⁵; -C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵;
35 C₁-C₄ alkyl; phenyl; and
5-6 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated;

5 R¹⁴ and R¹⁵ are independently selected from the group: H, methyl, and ethyl; and

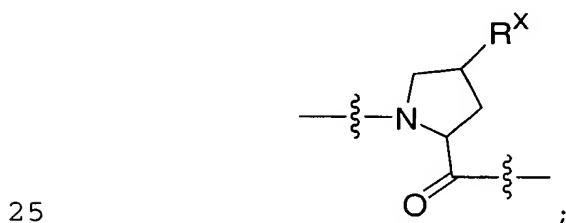
R¹⁶ is a bond, -O- or -S-.

10 [7] In another alternative embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein:

15 W is pinanediol boronic ester;

A is A²-A³-A⁴, A²-A³-A⁴-A⁵, or A²-A³-A⁴-A⁵-A⁶;

20 A² is Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val, Abu, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl), cyclohexylalanine, or



A³, A⁴, A⁵, and A⁶ are independently selected from an amino acid residue wherein said amino acid residue, at each occurrence, is independently selected from the group:

30 Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Gla; Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), Thr(OBzl), cyclohexylglycine,

35 cyclohexylalanine, cyclohexylglycine,

5 cyclopropylglycine, t-butylglycine, phenylglycine, and
3,3-diphenylalanine;

R^1 is $-\text{CH}_2\text{CH}_2-\text{R}^{1a}$ or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{R}^{1a}$;

10 R^{1a} is selected from the group: phenyl, 2-naphthyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-(1,1'-biphenyl)-, 2,5-dimethylphenyl, 2,4-dimethylphenyl, 3-CF₃-phenyl, 4-CF₃-phenyl, 2-F-phenyl, 3-F-phenyl, 4-F-phenyl, 4-Cl-phenyl, 4-Br-phenyl, 4-phenoxyphenyl,
15 4-isopropylphenyl, 4-cyclohexylphenyl, 4-tBu-phenyl, 4-methoxyphenyl, 2,6-diF-phenyl, 4-hydroxy-phenyl, (4-methoxyphenoxy)phenyl, methyl, ethyl, propyl, i-propyl, n-butyl, i-butyl, and cyclobutyl;

20 R^X is H or $-(\text{CH}_2)_m-\text{R}^{16}-(\text{CH}_2)_n-\text{R}^{12}$;

m and n are independently selected from 0 or 1;

R^2 is H or methyl;

25

R^3 is H, methyl, ethyl propyl, butyl, phenyl, benzyl, $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{CO}_2\text{R}^{11}$, $-\text{C}(=\text{O})\text{NHR}^{11}$ or acetyl;

R^{11} is C₁-C₄ alkyl substituted with 0-1 R^{11a} ,

30

phenyl substituted with 0-2 R^{11b} , or

5-6 membered heterocyclic ring system consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N; optionally saturated, partially unsaturated or unsaturated; said 5-6 membered
35 heterocyclic ring system is substituted with 0-2 R^{11b} ;

R^{11a} is methyl, ethyl propyl, butyl, F, Cl, Br, Cl, -OH, -OCH₃, -SH, -SCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, phenyl, or a
40 5-6 membered heterocyclic ring system containing 1, 2

5 or 3 heteroatoms selected from nitrogen, oxygen and sulfur;

R^{11b} is -NO₂, -NH₂, -SO₃H, -SO₂CH₃, -CO₂H, -CF₃, -OH, -SH,
-OCF₃, Cl, Br, I, F, =O, methyl, ethyl, propyl, butyl,
10 -OCH₃, -OCH₂CH₃, -SCH₃, -SCH₂CH₃, phenyl, or benzyl;

R¹² is selected from the group: H;
C₁-C₄ alkyl substituted with 0-2 R^{12a};
6-10 member aryl substituted with 0-3 R^{12a}; and
15 5-10 membered heterocyclic ring system consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N; optionally saturated, partially unsaturated or unsaturated; said 5-10 membered heterocyclic ring system is substituted with 0-2
20 R^{12a};

R^{12a} is independently selected from the group: -NO₂;
halogen; haloalkyl; carboxyl; carboxy(lower alkyl);
-OR¹⁴; -SR¹⁴; -NR¹⁴R¹⁵; -C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵;
25 C₁-C₄ alkyl; phenyl; and
5-6 membered heterocyclic ring system consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N; optionally saturated, partially unsaturated or unsaturated;

30

R¹⁴ and R¹⁵ are independently selected from the group: H, methyl, and ethyl; and

R¹⁶ is a bond, -O- or -S-.

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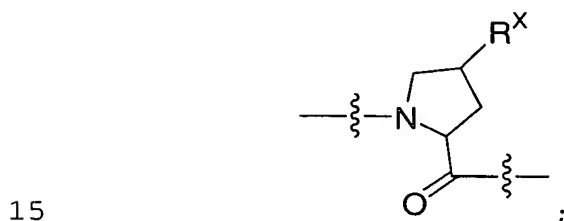
[8] In another alternative embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein:

40

5 W is pinanediol boronic ester;

A is A²-A³-A⁴, A²-A³-A⁴-A⁵, or A²-A³-A⁴-A⁵-A⁶;

10 A² is Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Hyp,
Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val,
Abu, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu),
Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl),
Hyp(OBzl), Thr(OBzl), cyclohexylalanine, or



A³, A⁴, A⁵, and A⁶ are independently selected from an amino
acid residue wherein said amino acid residue, at each
occurrence, is independently selected from the group:
20 Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Hyp, Ile,
Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val,
Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Gla;
Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl),
Hyp(OBzl), Thr(OBzl), cyclohexylglycine,
25 cyclohexylalanine, cyclohexylglycine,
cyclopropylglycine, t-butylglycine, phenylglycine, and
3,3-diphenylalanine;

30 R¹ is -CH₂CH₂-R^{1a} or -CH₂CH₂CH₂CH₂-R^{1a};

R^{1a} is selected from the group: phenyl, 2-naphthyl, 2-
methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-(1,1'-
biphenyl)-, 2,5-dimethylphenyl, 2,4-dimethylphenyl,
3-CF₃-phenyl, 4-CF₃-phenyl, 2-F-phenyl, 3-F-phenyl,

5 4-F-phenyl, 4-Cl-phenyl, 4-Br-phenyl, 4-phenoxyphenyl,
4-isopropylphenyl, 4-cyclohexylphenyl, 4-tBu-phenyl,
4-methoxyphenyl, 2,6-diF-phenyl, 4-hydroxy-phenyl,
(4-methoxyphenoxy)phenyl, methyl, ethyl, propyl,
i-propyl, n-butyl, i-butyl, and cyclobutyl;

10

R^X is H or benzoxy;

R^2 is H;

15 R^3 is H, $-C(=O)R^{11}$ or acetyl;

R^{11} is 5-6 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
20 unsaturated or unsaturated; said 5-6 membered
heterocyclic ring system is substituted with 0-2 R^{11b} ;
and

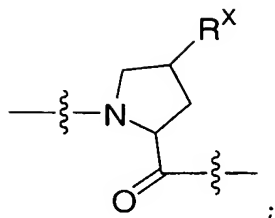
R^{11b} is $-NO_2$, $-NH_2$, $-SO_3H$, $-SO_2CH_3$, $-CO_2H$, $-CF_3$, $-OH$, $-SH$,
25 $-OCF_3$, Cl, Br, F, methyl, ethyl, propyl, butyl, $-OCH_3$,
or $-OCH_2CH_3$.

[9] In another alternative embodiment, the present
invention provides a compound of Formula (I) or a
30 pharmaceutically acceptable salt or prodrug thereof,
wherein:

W is pinanediol boronic ester;

35 A is $A^2-A^3-A^4$, $A^2-A^3-A^4-A^5$, or $A^2-A^3-A^4-A^5-A^6$;

A^2 is Pro, Leu, Asp, Abu, Val, cyclohexylalanine, or



5

A^3 is Val, Glu, Ile, Thr, cyclohexylglycine, or cyclohexylalanine;

10 A^4 is Val, Ile, Leu, cyclohexylglycine, cyclopropylglycine, t-butylglycine, phenylglycine, or 3,3-diphenylalanine;

A^5 is Asp, Glu, Val, Ile, t-butylglycine or Gla;

15 A^6 is Asp or Glu;

R^1 is $-\text{CH}_2\text{CH}_2-\text{R}^{1a}$ or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{R}^{1a}$;

20 R^{1a} is selected from the group: phenyl, 2-naphthyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-(1,1'-biphenyl)-, 2,5-dimethylphenyl, 2,4-dimethylphenyl, 3-CF₃-phenyl, 4-CF₃-phenyl, 2-F-phenyl, 3-F-phenyl, 4-F-phenyl, 4-Cl-phenyl, 4-Br-phenyl, 4-phenoxyphenyl, 4-isopropylphenyl, 4-cyclohexylphenyl, 4-tBu-phenyl, 25 4-methoxyphenyl, 2,6-diF-phenyl, 4-hydroxy-phenyl, (4-methoxyphenoxy)phenyl, methyl, ethyl, propyl, i-propyl, n-butyl, i-butyl, and cyclobutyl;

R^X is H or $-(\text{CH}_2)_m-\text{R}^{16}-(\text{CH}_2)_n-\text{R}^{12}$;

30

m and n are independently selected from 0 or 1;

R^2 is H or methyl;

35 R^3 is H, methyl, ethyl, propyl, butyl, phenyl, benzyl, $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{CO}_2\text{R}^{11}$, $-\text{C}(=\text{O})\text{NHR}^{11}$ or acetyl;

5

R^{11} is C_1 - C_4 alkyl substituted with 0-1 R^{11a} ,
phenyl substituted with 0-2 R^{11b} , or
5-6 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-6 membered
heterocyclic ring system is substituted with 0-2
 R^{11b} ;

10

15 R^{11a} is methyl, ethyl propyl, butyl, F, Cl, Br, Cl, -OH,
-OCH₃, -SH, -SCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, phenyl, or a
5-6 membered heterocyclic ring system containing 1, 2
or 3 heteroatoms selected from nitrogen, oxygen and
sulfur;

20

R^{11b} is -NO₂, -NH₂, -SO₃H, -SO₂CH₃, -CO₂H, -CF₃, -OH, -SH,
-OCF₃, Cl, Br, I, F, =O, methyl, ethyl, propyl, butyl,
-OCH₃, -OCH₂CH₃, -SCH₃, -SCH₂CH₃, phenyl, or benzyl;

25 R^{12} is selected from the group: H;

C_1 - C_4 alkyl substituted with 0-2 R^{12a} ;

6-10 member aryl substituted with 0-3 R^{12a} ; and

5-10 membered heterocyclic ring system consisting of
carbon atoms and 1-4 heteroatoms selected from the

30 group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated; said 5-10 membered
heterocyclic ring system is substituted with 0-2
 R^{12a} ;

35 R^{12a} is independently selected from the group: -NO₂;
halogen; haloalkyl; carboxyl; carboxy(lower alkyl);
-OR¹⁴; -SR¹⁴; -NR¹⁴R¹⁵; -C(=O)NR¹⁴R¹⁵; -NR¹⁴C(=O)R¹⁵;
 C_1 - C_4 alkyl; phenyl; and

5-6 membered heterocyclic ring system consisting of

40 carbon atoms and 1-4 heteroatoms selected from the

5 group: O, S, and N; optionally saturated, partially
unsaturated or unsaturated;

R¹⁴ and R¹⁵ are independently selected from H, methyl, or
ethyl; and

10

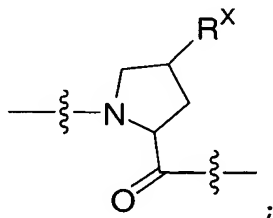
R¹⁶ is a bond, -O- or -S-.

[10] In another alternative embodiment, the present
invention provides a compound of Formula (I) or a
15 pharmaceutically acceptable salt or prodrug thereof,
wherein:

W is pinanediol boronic ester;

20 A is A²-A³-A⁴, A²-A³-A⁴-A⁵, or A²-A³-A⁴-A⁵-A⁶;

A² is Pro, Leu, Asp, Abu, Val, cyclohexylalanine, or



25

A³ is Val, Glu, Ile, Thr, cyclohexylglycine, or
cyclohexylalanine;

A⁴ is Val, Ile, Leu, cyclohexylglycine, cyclopropylglycine,
30 t-butylglycine, phenylglycine, or 3,3-diphenylalanine;

A⁵ is Asp, Glu, Val, Ile, t-butylglycine or Gla;

A⁶ is Asp or Glu;

35

R¹ is -CH₂CH₂-R^{1a} or -CH₂CH₂CH₂CH₂-R^{1a};

5

R^{1a} is selected from the group: phenyl, 2-naphthyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-(1,1'-biphenyl)-, 2,5-dimethylphenyl, 2,4-dimethylphenyl, 3-CF₃-phenyl, 4-CF₃-phenyl, 2-F-phenyl, 3-F-phenyl, 10 4-F-phenyl, 4-Cl-phenyl, 4-Br-phenyl, 4-phenoxyphenyl, 4-isopropylphenyl, 4-cyclohexylphenyl, 4-tBu-phenyl, 4-methoxyphenyl, 2,6-diF-phenyl, 4-hydroxy-phenyl, (4-methoxyphenoxy)phenyl, methyl, ethyl, propyl, i-propyl, n-butyl, i-butyl, and cyclobutyl;

15

R^x is H or benzoxy;

R² is H;

20 R³ is H, -C(=O)R¹¹ or acetyl;

R¹¹ is 5-6 membered heterocyclic ring system consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N; optionally saturated, partially 25 unsaturated or unsaturated; said 5-6 membered heterocyclic ring system is substituted with 0-2 R^{11b}; and

R^{11b} is -NO₂, -NH₂, -SO₃H, -SO₂CH₃, -CO₂H, -CF₃, -OH, -SH, 30 -OCF₃, Cl, Br, F, methyl, ethyl, propyl, butyl, -OCH₃, or -OCH₂CH₃.

It is understood that any and all embodiments of the present invention may be taken in conjunction with any 35 other embodiment to describe additional even more preferred embodiments of the present invention.

5 [11] In another alternative embodiment, the present invention provides a compound, or a stereoisomer or a pharmaceutically acceptable salt form or prodrug thereof, selected from:

10 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester;

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-4-phenylbutylboronic acid (+)-pinanediol ester;

15 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-5-phenylpentylboronic acid (+)-pinanediol ester;

20 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2-naphthyl)propylboronic acid (+)-pinanediol ester;

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2-methyl)phenylpropylboronic acid (+)-pinanediol ester;

25 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(3-methyl)phenylpropylboronic acid (+)-pinanediol ester;

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-methyl)phenylpropylboronic acid (+)-pinanediol ester;

30 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(1,1'-biphenyl)-4-ylpropylboronic acid (+)-pinanediol ester;

35 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2,5-dimethyl)phenylpropylboronic acid (+)-pinanediol ester;

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2,4-dimethyl)phenylpropylboronic acid (+)-pinanediol ester;

45

- 5 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(4-trifluoromethyl)phenylpropylboronic acid (+)-pinanediol ester;
- 10 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(3-trifluoromethyl)phenylpropylboronic acid (+)-pinanediol ester;
- 15 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(4-fluoro)phenylpropylboronic acid (+)-pinanediol ester;
- 20 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(4-isopropyl)phenylpropylboronic acid (+)-pinanediol ester;
- 25 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(4-cyclohexyl)phenylpropylboronic acid (+)-pinanediol ester;
- 30 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(4-*tert*-butyl)phenylpropylboronic acid (+)-pinanediol ester;
- 35 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(4-methoxy)phenylpropylboronic acid (+)-pinanediol ester;
- 40 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(4-chloro)phenylpropylboronic acid (+)-pinanediol ester;
- 45 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(2-fluoro)phenylpropylboronic acid (+)-pinanediol ester;

5 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(3-fluoro)phenylpropylboronic acid (+)-pinanediol ester;

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2,6-difluoro)phenylpropylboronic acid (+)-pinanediol ester;

10

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-hydroxy)phenylpropylboronic acid (+)-pinanediol ester;

15

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-5-hexylboronic acid (+)-pinanediol ester;

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-5-methylhexylboronic acid (+)-pinanediol ester;

20

H-Asp-Glu-Val-Val-Pro-(1R)-1-aminoheptylboronic acid (+)-pinanediol ester;

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-4-cyclobutylbutylboronic acid (+)-pinanediol ester; and

25

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-5-ethylheptylboronic acid (+)-pinanediol ester.

[12] In another alternative embodiment, the present invention provides a compound, or a stereoisomer or a pharmaceutically acceptable salt form or prodrug thereof, selected from:

35 Ac-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester;

Ac-Val-Pro-(1R)-1-amino-3-(4-trifluoromethyl)phenylpropylboronic acid (+)-pinanediol ester;

40 Ac-Val-Pro-(1R)-1-amino-3-(4-phenoxy)phenylpropylboronic acid (+)-pinanediol ester;

5

Ac-Val-Pro-(1R)-1-amino-3-(4-hydroxy)phenylpropylboronic acid (+)-pinanediol ester;

10

Ac-Val-Pro-(1R)-1-amino-3-(4-(4-methoxyphenoxy)phenyl)propylboronic acid (+)-pinanediol ester;

Ac-Val-Pro-(1R)-1-amino-3-(4-(4-methylphenoxy)phenyl)propylboronic acid (+)-pinanediol ester; and

15

(2-pyrazinecarbonyl)-Val-Val-Hyp(OBn)-(1R)-1-amino-3-(4-trifluoromethyl)phenylpropylboronic acid (+)-pinanediol ester.

20

This invention also provides compositions comprising one or more of the foregoing compounds and methods of using such compositions in the treatment of hepatitis C virus, such as inhibition of hepatitis C virus protease, in mammals or as reagents used as inhibitors of hepatitis C virus protease in the processing of blood to plasma for diagnostic and other commercial purposes.

25

30

In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides a method of treating a viral infection which comprises administering to a host in need of such treatment a therapeutically effective amount of compounds of Formula (I) or pharmaceutically acceptable salt forms or prodrug thereof.

35

40

In another embodiment, the present invention provides A method of treating HCV which comprises administering to a host in need of such treatment a therapeutically effective

- 5 amount of compounds of Formula (I) or pharmaceutically acceptable salt forms or prodrug thereof.

DEFINITIONS

- 10 As used throughout the specification, the following abbreviations for amino acid residues or amino acids apply:

- Abu is L-aminobutyric acid;
Ala is L-alanine;
15 Alg is L-2-amino-4-pentenoic acid;
Ape is L-2-aminopentanoic acid;
Arg is L-arginine;
Asn is L-asparagine;
Asp is L-aspartic acid;
20 Aze is azedine-2-carboxylic acid;
Cha is L-2-amino-3-cyclohexylpropionic acid;
Cpa is L-2-amino-3-cyclopropylpropionic acid
Cpg is L-2-amino-2-cyclopropylacetic acid;
Cys is L-cysteine;
25 Dfb is L-4,4'-difluoro-1-amino-butyric acid;
Dpa is L-2-amino-3,3-diphenylpropionic acid;
Gla is gamma-carboxyglutamic acid;
Gln is L-glutamine;
Glu is L-glutamic acid;
30 Gly is glycine;
His is L-histidine;
HomoLys is L-homolysine;
Hyp is L-4-hydroxyproline;
Ile is L-isoleucine;
35 Irg is isothiuronium analog of L-Arg;
Leu is L-leucine;
Lys is L-lysine;
Met is L-methionine;
Orn is L-ornithine;
40 Phe is L-phenylalanine;
Phe(4-fluoro) is para-fluorophenylalanine;

5 Pro is L-proline;
Sar is L-sarcosine;
Ser is L-serine;
Thr is L-threonine;
Tpa is L-2-amino-5,5,5-trifluoropentanoic acid;
10 Trp is L-tryptophan;
Tyr is L-tyrosine; and
Val is L-valine.

The "D" prefix for the foregoing abbreviations
15 indicates the amino acid is in the D-configuration. "D,L"
indicates the amino is present in mixture of the D- and the
L-configuration. The prefix "boro" indicates amino acid
residues where the carboxyl is replaced by a boronic acid
or a boronic ester. For example, if R¹ is isopropyl and Y¹
20 and Y² are OH, the C-terminal residue is abbreviated
"boroVal-OH" where "-OH" indicates the boronic acid is in
the form of the free acid. The pinanediol boronic ester and
the pinacol boronic ester are abbreviated "-C₁₀H₁₆" and
"-C₆H₁₂", respectively. Examples of other useful diols for
25 esterification with the boronic acids are 1,2-ethanediol,
1,3-propanediol, 1,2-propanediol, 2,3-butanediol, 1,2-
diisopropylethanediol, 5,6-decanediol, and 1,2-
dicyclohexylethanediol. Analogs containing sidechain
substituents are described by indicating the substituent in
30 parenthesis following the name of the parent residue. For
example the analog of boroPhenylalanine containing a meta
cyano group is -boroPhe(mCN)-.

The following abbreviations may also be used herein
and are defined as follows. The abbreviation "DIBAL" means
35 diisobutylaluminum hydride. The abbreviation "RaNi" means
Raney nickel. The abbreviation "LAH" means lithium aluminum
hydride. The abbreviation "1,1'-CDI" means 1,1'-
carbonyldiimidazole. The abbreviation "Bn" means benzyl.
The abbreviation "BOC" means t-butyl carbamate. The
40 abbreviation "CBZ" means benzyl carbamate. Other
abbreviations are: "BSA", benzene sulfonic acid; "THF",

5 tetrahydrofuran; "DMF", dimethylformamide; "EDCI", 1-
dimethylaminopropyl-3-ethylcarbodiimide hydrochloride;
"HOAt", 1-hydroxy-7-azabenzotriazole; "DIEA", N,N-
diisopropylethylamine; "Boc-", t-butoxycarbonyl-; "Ac-",
acetyl; "pNA", p-nitro-aniline; "DMAP", 4-N,N-
10 dimethylaminopyridine; "Tris",
Tris(hydroxymethyl)aminomethane; "PyAOP", 7-
azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium
hexafluorophosphate; "MS", mass spectrometry; "FAB/MS",
fast atom bombardment mass spectrometry. LRMS(NH₃ -CI) and
15 HRMS(NH₃ -CI) are low and high resolution mass spectrometry,
respectively, using NH₃ as an ion source.

The compounds herein described may have asymmetric
centers. All chiral, diastereomeric, and racemic forms are
included in the present invention. Many geometric isomers
20 of olefins, C=N double bonds, and the like can also be
present in the compounds described herein, and all such
stable isomers are contemplated in the present invention.
It will be appreciated that certain compounds of the
present invention contain an asymmetrically substituted
25 carbon atom, and may be isolated in optically active or
racemic forms. It is well known in the art how to prepare
optically active forms, such as by resolution of racemic
forms or by synthesis, from optically active starting
materials. Also, it is realized that cis and trans
30 geometric isomers of the compounds of the present invention
are described and may be isolated as a mixture of isomers
or as separated isomeric forms. All chiral,
diastereomeric, racemic forms and all geometric isomeric
forms of a structure are intended, unless the specific
35 stereochemistry or isomer form is specifically indicated.

The reactions of the synthetic methods claimed herein
are carried out in suitable solvents which may be readily
selected by one skilled in the art of organic synthesis,
said suitable solvents generally being any solvent which is
40 substantially nonreactive with the starting materials
(reactants), the intermediates, or products at the

5 temperatures at which the reactions are carried out. A given reaction may be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step may be selected.

10 Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By stable compound or stable structure it is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious
15 therapeutic agent.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that
20 the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then two hydrogens on the atom are replaced.

When any variable (e.g., R^7 or R^{13}) occurs more than
25 one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^{13} , then said group may optionally be substituted with up to three
30 R^{13} groups and R^{13} at each occurrence is selected independently from the definition of R^{13} . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By stable compound it is meant herein a compound
35 that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is
40 listed without indicating the atom via which such substituent is bonded to the rest of the compound of a

5 given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

10 In Formula (I) the substituent A is intended to be a peptide of 2 to 6 amino acid residues. For example, the scope of A can be described as A^2-A^3 , $A^2-A^3-A^4$, $A^2-A^3-A^4-A^5$, $A^2-A^3-A^4-A^5-A^6$, $A^2-A^3-A^4-A^5-A^6-A^7$. Alternatively, A can be described as $(A'')_n$ wherein n is 2, 3, 4, 5, or 6. By either description when A is comprised of two amino acid
15 residues or greater, each amino acid residue of A is independently selected apart from each other amino acid residue. For example, A^2 , A^3 , A^4 , A^5 , A^6 , and A^7 are independently selected from the defined list of possible amino acid residues, including modified or unnatural amino
20 acid residues, disclosed herein. Likewise, each A'' , when n is 2 or greater, is independently selected from the defined list of possible amino acid residues, including modified or unnatural amino acid residues, disclosed herein.

"Amino acid residue" as used herein, refers to
25 natural, modified or unnatural amino acids of either D- or L-configuration and means an organic compound containing both a basic amino group and an acidic carboxyl group. Natural amino acids residues are Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Orn, Phe,
30 Pro, Sar, Ser, Thr, Trp, Tyr, and Val. Roberts and Vellaccio, The Peptides, Vol 5; 341-449 (1983), Academic Press, New York, discloses numerous suitable unnatural amino acids and is incorporated herein by reference for that purpose. Additionally, said reference describes, but
35 does not extensively list, acyclic N-alkyl and acyclic α,α -disubstituted amino acids. Included in the scope of the present invention are N-alkyl, aryl, and alkylaryl analogs of both in chain and N-terminal amino acid residues. Similarly, alkyl, aryl, and alkylaryl maybe substituted for

- 5 the alpha hydrogen. Illustrated below are examples of N-alkyl and alpha alkyl amino acid residues, respectively.



- Modified amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, 3-hydroxyproline, an N-CBZ-protected amino acid, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, 3,3-diphenylalanine, naphthylalanine, phenylglycine, β -phenylproline, tert-leucine, cyclohexylalanine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, t-butylglycine, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, 2-benzyl-5-aminopentanoic acid.

25

- Unnatural amino acids that fall within the scope of this invention are by way of example and without limitation: 2-aminobutanoic acid, 2-aminopentanoic acid, 2-aminohexanoic acid, 2-aminoheptanoic acid, 2-aminooctanoic acid, 2-aminononanoic acid, 2-aminodecanoic acid, 2-aminoundecanoic acid, 2-amino-3,3-dimethylbutanoic acid, 2-amino-4,4-dimethylpentanoic acid, 2-amino-3-methylhexanoic acid, 2-amino-3-methylheptanoic acid, 2-amino-3-methyloctanoic acid, 2-amino-3-methylnonanoic acid, 2-amino-4-methylhexanoic acid, 2-amino-3-ethylpentanoic acid, 2-amino-3,4-dimethylpentanoic acid, 2-amino-3,5-dimethylhexanoic acid, 2-amino-3,3-dimethylpentanoic acid,

35

- 5 2-amino-3-ethyl-3-methylpentanoic acid, 2-amino-3,3-diethylpentanoic acid, 2-amino-5-methylhexanoic acid, 2-amino-6-methylheptanoic, 2-amino-7-methyloctanoic, 2-amino-2-cyclopentylacetic, 2-amino-2-cyclohexylacetic acid, 2-amino-2-(1-methylcyclohexyl)acetic acid, 2-amino-2-(2-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(3-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(4-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(1-ethylcyclohexyl)acetic acid, 2-amino-3-(cyclohexyl)propanoic acid, 2-amino-4-(cyclohexyl)butanoic acid, 2-amino-3-(1-adamantyl)propanoic acid, 2-amino-3-butenic acid, 2-amino-3-methyl-3-butenic acid, 2-amino-4-pentenoic acid, 2-amino-4-hexenoic acid, 2-amino-5-heptenoic acid, 2-amino-4-methyl-4-hexenoic acid, 2-amino-5-methyl-4-hexenoic acid, 2-amino-4-methyl-5-hexenoic acid, 2-amino-6-heptenoic acid, 2-amino-3,3,4-trimethyl-4-pentenoic acid, 2-amino-4-chloro-4-pentenoic, 2-amino-4,4-dichloro-3-butenic acid, 2-amino-3-(2-methylenecyclopropyl)-propanoic acid, 2-amino-2-(2-cyclopentenyl)acetic acid, 2-amino-2-(cyclohexenyl)acetic acid, 2-amino-3-(2-cyclopentenyl)propanoic acid, 2-amino-3-(3-cyclopentenyl)propanoic acid, 2-amino-3-(1-cyclohexyl)propanoic acid, 2-amino-2-(1-cyclopentenyl)acetic acid, 2-amino-2-(1-cyclohexyl)acetic acid, 2-amino-2-(1-cycloheptenyl)acetic acid, 2-amino-2-(1-cyclooctenyl)acetic acid, 2-amino-3-(1-cycloheptenyl)propanoic acid, 2-amino-3-(1,4-cyclohexadienyl)propanoic acid, 2-amino-3-(2,5-cyclohexadienyl)propanoic acid, 2-amino-2-(7-cycloheptatrienyl)acetic acid, 2-amino-4,5-hexadienoic acid, 2-amino-3-butyric acid, 2-amino-4-pentynoic acid, 2-amino-4-hexynoic acid, 2-amino-4-hepten-6-ynoic acid, 2-amino-3-fluoropropanoic acid, 2-amino-3,3,3-trifluoropropanoic acid, 2-amino-3-fluorobutanoic acid, 2-amino-3-fluoropentanoic acid, 2-amino-3-fluorohexanoic acid, 2-amino-3,3-difluorobutanoic acid, 2-amino-3,3-difluoro-3-phenylpropanoic acid, 2-amino-3-

- 5 perfluoroethylpropanoic acid, 2-amino-3-perfluoropropylpropanoic acid, 2-amino-3-fluoro-3-methylbutanoic acid, 2-amino-5,5,5-trifluoropentanoic acid, 2-amino-3-methyl-4,4,4-trifluorobutanoic acid, 2-amino-3-trifluoromethyl-4,4,4-trifluorobutanoic acid, 2-amino-10 3,3,4,4,5,5-heptafluoropentanoic acid, 2-amino-3-methyl-5-fluoropentanoic acid, 2-amino-3-methyl-4-fluoropentanoic acid, 2-amino-5,5-difluorohexanoic acid, 2-amino-4-(fluoromethyl)-5-fluoropentanoic acid, 2-amino-4-trifluoromethyl-5,5,5-trifluoropentanoic acid, 2-amino-3-15 fluoro-3-methylbutanoic acid, 2-amino-3-fluoro-3-phenylpentanoic acid, 2-amino-2-(1-fluorocyclopentyl)acetic acid, 2-amino-2-(1-fluorocyclohexyl)acetic acid, 2-amino-3-chloropropanoic acid, 2-amino-3-chlorobutanoic acid, 2-amino-4,4-dichlorobutanoic acid, 2-amino-4,4,4-20 trichlorobutanoic acid, 2-amino-3,4,4-trichlorobutanoic acid, 2-amino-6-chlorohexanoic acid, 2-amino-4-bromobutanoic acid, 2-amino-3-bromobutanoic acid, 2-amino-3-mercaptobutanoic acid, 2-amino-4-mercaptobutanoic acid, 2-amino-3-mercapto-3,3-dimethylpropanoic acid, 2-amino-3-25 mercapto-3-methylpentanoic acid, 2-amino-3-mercaptopentanoic acid, 2-amino-3-mercapto-4-methylpentanoic acid, 2-amino-3-methyl-4-mercaptopentanoic acid, 2-amino-5-mercapto-5-methylhexanoic acid, 2-amino-2-(1-mercaptocyclobutyl)acetic acid, 2-amino-2-(1-30 mercaptocyclopentyl)acetic acid, 2-amino-2-(1-mercaptocyclohexyl)acetic acid, 2-amino-5-(methylthio)pentanoic acid, 2-amino-6-(methylthio)hexanoic acid, 2-amino-4-methylthio-3-phenylbutanoic acid, 2-amino-5-ethylthio-5-methylpentanoic acid, 2-amino-5-ethylthio-35 3,5,5-trimethylpentanoic acid, 2-amino-5-ethylthio-5-phenylpentanoic acid, 2-amino-5-ethylthio-5-pentanoic acid, 2-amino-5-butylthio-5-methylpentanoic acid, 2-amino-5-butylthio-3,5,5-trimethylpentanoic acid, 2-amino-5-butylthio-5-phenylpentanoic acid, 2-amino-5-40 (butylthio)pentanoic acid, 2-amino-3-methyl-4-hydroselenopentanoic acid, 2-amino-4-methylselenobutanoic

- 5 acid, 2-amino-4-ethylselenobutanoic acid, 2-amino-4-benzylselenobutanoic acid, 2-amino-3-methyl-4-(methylseleno)butanoic acid, 2-amino-3-(aminomethylseleno)propanoic acid, 2-amino-3-(3-aminopropylseleno)propanoic acid, 2-amino-4-methyltellurobutanoic acid, 2-amino-4-hydroxybutanoic acid, 2-amino-4-hydroxyhexanoic acid, 2-amino-3-hydroxypentanoic acid, 2-amino-3-hydroxyhexanoic acid, 2-amino-3-methyl-4-hydroxybutanoic acid, 2-amino-3-hydroxy-3-methylbutanoic acid, 2-amino-6-hydroxyhexanoic acid, 2-amino-4-hydroxyhexanoic acid, 2-amino-3-hydroxy-4-methylpentanoic acid, 2-amino-3-hydroxy-3-methylpentanoic acid, 2-amino-4-hydroxy-3,3-dimethylbutanoic acid, 2-amino-3-hydroxy-4-methylpentanoic acid, 2-amino-3-hydroxybutanedioic acid, 2-amino-3-hydroxy-3-phenylpropanoic acid, 2-amino-3-hydroxy-3-(4-nitrophenyl)propanoic acid, 2-amino-3-hydroxy-3-(3-pyridyl)propanoic acid, 2-amino-2-(1-hydroxycyclopropyl)acetic acid, 2-amino-3-(1-hydroxycyclohexyl)propanoic acid, 2-amino-3-hydroxy-3-phenylpropanoic acid, 2-amino-3-hydroxy-3-[3-bis(2-chloroethyl)aminophenyl]propanoic acid, 2-amino-3-hydroxy-3-(3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-hydroxy-3-(3,4-methylenedioxyphenyl)propanoic acid, 2-amino-4-fluoro-3-hydroxybutanoic acid, 2-amino-4,4,4-trichloro-3-hydroxybutanoic acid, 2-amino-3-hydroxy-4-hexynoic acid, 2-amino-3,4-dihydroxybutanoic acid, 2-amino-3,4,5,6-tetrahydroxyhexanoic acid, 2-amino-4,5-dihydroxy-3-methylpentanoic acid, 2-amino-5,6-dihydroxyhexanoic acid, 2-amino-5-hydroxy-4-(hydroxymethyl)pentanoic acid, 2-amino-4,5-dihydroxy-4-(hydroxymethyl)pentanoic acid, 2-amino-3-hydroxy-5-benzyloxypentanoic acid, 2-amino-3-(2-aminoethoxy)propanoic acid, 2-amino-4-(2-aminoethoxy)butanoic acid, 2-amino-4-oxobutanoic acid, 2-amino-3-oxobutanoic acid, 2-amino-4-methyl-3-oxopentanoic acid, 2-amino-3-phenyl-3-oxopropanoic acid, 2-amino-4-phenyl-3-oxobutanoic acid, 2-amino-3-methyl-4-oxopentanoic acid, 2-amino-4-oxo-4-(4-hydroxyphenyl)butanoic acid, 2-

- 5 amino-4-oxo-4-(2-furyl)butanoic acid, 2-amino-4-oxo-4-(2-nitrophenyl)butanoic acid, 2-amino-4-oxo-4-(2-amino-4-chlorophenyl)butanoic acid, 2-amino-3-(4-oxo-1-cyclohexenyl)propanoic acid, 2-amino-3-(4-oxocyclohexanyl)propanoic acid, 2-amino-3-(2,5-dimethyl-10 3,6-dioxo-1,4-cyclohexadienyl)propanoic acid, 2-amino-3-(1-hydroxy-5-methyl-7-oxo-cyclohepta-1,3,5-trien-2-yl)propanoic acid, 2-amino-3-(1-hydroxy-7-oxo-cyclohepta-1,3,5-trien-3-yl)propanoic acid, 2-amino-3-(1-hydroxy-7-oxo-cyclohepta-1,3,5-trien-4-yl)propanoic acid, 2-amino-4-15 methoxy-3-butenic acid, 2-amino-4-(2-aminoethoxy)-3-butenic acid, 2-amino-4-(2-amino-3-hydroxypropyl)-3-butenic acid, 2-amino-2-(4-methoxy-1,4-cyclohexadienyl)acetic acid, 2-amino-3,3-diethoxypropanoic acid, 2-amino-4,4-dimethylbutanoic acid, 2-amino-2-(2,3-20 epoxycyclohexyl)acetic acid, 2-amino-3-(2,3-epoxycyclohexyl)propanoic acid, 2-amino-8-oxo-9,10-epoxydecanoic acid, 2-amino-propanedioic acid, 2-amino-3-methylbutanedioic acid, 2-amino-3,3-dimethylbutanedioic acid, 2-amino-4-methylpentanedioic acid, 2-amino-3-25 methylpentanedioic acid, 2-amino-3-phenylpentanedioic acid, 2-amino-3-hydroxypentanedioic acid, 2-amino-3-carboxypentanedioic acid, 2-amino-4-ethylpentanedioic acid, 2-amino-4-propylpentanedioic acid, 2-amino-4-isoamylpentanedioic acid, 2-amino-4-phenylpentanedioic acid, 2-amino-hexanedioic acid, 2-amino-heptanedioic acid, 2-amino-decanedioic acid, 2-amino-octanedioic acid, 2-amino-dodecanedioic acid, 2-amino-3-methylenebutanedioic acid, 2-amino-4-methylenepentanedioic acid, 2-amino-3-30 fluorobutanedioic acid, 2-amino-4-fluoropentanedioic acid, 2-amino-3,3-difluorobutanedioic acid, 2-amino-3-chloropentanedioic acid, 2-amino-3-hydroxybutanedioic acid, 2-amino-4-hydroxypentanedioic acid, 2-amino-4-hydroxyhexanedioic acid, 2-amino-3,4-dihydroxypentanedioic acid, 2-amino-3-(3-hydroxypropyl)butanedioic acid, 2-amino-40 3-(1-carboxy-4-hydroxy-2-cyclodienyl)propanoic acid, 2-amino-3-(aceto)butanedioic acid, 2-amino-3-cyanobutanedioic

- 5 acid, 2-amino-3-(2-carboxy-6-oxo-6H-pyran-5-yl)propanoic acid, 2-amino-3-carboxybutanedioic acid, 2-amino-4-carboxypentanedioic acid, 3-amido-2-amino-3-hydroxypropanoic acid, 3-amido-2-amino-3-methylpropanoic acid, 3-amido-2-amino-3-phenylpropanoic acid, 3-amido-2,3-
- 10 diaminopropanoic acid, 3-amido-2-amino-3-[N-(4-hydroxyphenyl)amino]propanoic acid, 2,3-diaminopropanoic acid, 2,3-diaminobutanoic acid, 2,4-diaminobutanoic acid, 2,4-diamino-3-methylbutanoic acid, 2,4-diamino-3-phenylbutanoic acid, 2-amino-3-(methylamino)butanoic acid,
- 15 2,5-diamino-3-methylpentanoic acid, 2,7-diaminoheptanoic acid, 2,4-diaminoheptanoic acid, 2-amino-2-(2-piperidyl)acetic acid, 2-amino-2-(1-aminocyclohexyl)acetic acid, 2,3-diamino-3-phenylpropanoic acid, 2,3-diamino-3-(4-hydroxyphenyl)propanoic acid, 2,3-diamino-3-(4-
- 20 methoxyphenyl)propanoic acid, 2,3-diamino-3-[4-(N,N'-dimethylamino)phenyl]propanoic acid, 2,3-diamino-3-(3,4-dimethoxyphenyl)propanoic acid, 2,3-diamino-3-(3,4-methylenedioxyphenyl)propanoic acid, 2,3-diamino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid, 2,3-diamino-3-(2-
- 25 phenylethyl)propanoic acid, 2,3-diamino-3-propylpropanoic acid, 2,6-diamino-4-hexenoic acid, 2,5-diamino-4-fluoropentanoic acid, 2,6-diamino-5-fluorohexanoic acid, 2,6-diamino-4-hexynoic acid, 2,6-diamino-5,5-difluorohexanoic acid, 2,6-diamino-5,5-dimethylhexanoic
- 30 acid, 2,5-diamino-3-hydroxypentanoic acid, 2,6-diamino-3-hydroxyhexanoic acid, 2,5-diamino-4-hydroxypentanoic acid, 2,6-diamino-4-hydroxyhexanoic acid, 2,6-diamino-4-oxohexanoic acid, 2,7-diaminooctanedioic acid, 2,6-diamino-3-carboxyhexanoic acid, 2,5-diamino-4-carboxypentanoic
- 35 acid, 2-amino-4-(2-(N,N'-diethylamino)ethyl)pentandioic acid, 2-amino-4-(N,N'-diethylamino)pentandioic acid, 2-amino-4-(N-morpholino)pentandioic acid, 2-amino-4-(N,N'-bis(2-chloroethyl)amino)pentandioic acid, 2-amino-4-(N,N'-bis(2-hydroxyethyl)amino)pentandioic acid, 2,3,5-
- 40 triaminopentanoic acid, 2-amino-3-(N-(2-aminethyl)amino)propanoic acid, 2-amino-3-((2-

- 5 aminoethyl)seleno)propanoic acid, 2-amino-3-[(2-aminoethyl)thio]propanoic acid, 2-amino-4-aminooxybutanoic acid, 2-amino-5-hydroxyaminopentanoic acid, 2-amino-5-[N-(5-nitro-2-pyrimidinyl)amino]pentanoic acid, 2-amino-4-[(7-nitro-2,1,3-benzoxadiazol-4-yl)amino]butanoic acid, 2-
- 10 amino-3-guanidinopropanoic acid, 2-amino-3-guanidinobutanoic acid, 2-amino-4-guanidobutanoic acid, 2-amino-6-guanidohexanoic acid, 2-amino-6-ureidohexanoic acid, 2-amino-3-(2-iminoimidiazolin-4-yl)propanoic acid, 2-amino-2-(2-iminohexahydropyrimidin-4-yl)acetic acid, 2-
- 15 amino-3-(2-iminohexahydropyrimidin-4-yl)propanoic acid, 2-amino-4-fluoro-5-guanidopentanoic acid, 2-amino-4-hydroxy-5-guanidopentanoic acid, 2-amino-4-guanidooxybutanoic acid, 2-amino-6-amidinohexanoic acid, 2-amino-5-(N-acetimidoethylamino)pentanoic acid, 1-
- 20 aminocyclopropanecarboxylic acid, 1-amino-4-ethylcyclopropanecarboxylic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopentanecarboxylic acid, 1-amino-2,2,5,5-tetramethyl-cyclohexanecarboxylic acid, 1-
- 25 aminocycloheptanecarboxylic acid, 1-aminocyclononanecarboxylic acid, 2-aminoindan-2-carboxylic acid, 2-aminonorbornane-2-carboxylic acid, 2-amino-3-phenylnorbornane-2-carboxylic acid, 3-aminotetrahydrothiophene-3-carboxylic acid, 1-amino-1,3-
- 30 cyclohexanedicarboxylic acid, 3-aminopyrrolidine-3-carboxylic acid, 1,4-diaminocyclohexanecarboxylic acid, 6-alkoxy-3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 2-aminobenzobicyclo[2,2,2]octane-2-carboxylic acid, 2-aminoindan-2-carboxylic acid, 1-amino-2-(3,4-
- 35 dihydroxyphenyl)cyclopropanecarboxylic acid, 5,6-dialkoxy-2-aminoindane-2-carboxylic acid, 4,5-dihydroxy-2-aminoindan-2-carboxylic acid, 5,6-dihydroxy-2-aminotetralin-2-carboxylic acid, 2-amino-2-cyanoacetic acid, 2-amino-3-cyanopropanoic acid, 2-amino-4-cyanobutanoic acid, 2-amino-
- 40 5-nitropentanoic acid, 2-amino-6-nitrohexanoic acid, 2-amino-4-aminooxybutanoic acid, 2-amino-3-(N-

- 5 nitrosohydroxyamino)propanoic acid, 2-amino-3-ureidopropanoic acid, 2-amino-4-ureidobutanoic acid, 2-amino-3-phosphopropanoic acid, 2-amino-3-thiophosphopropanoic acid, 2-amino-4-methanephosphonylbutanoic acid, 2-amino-3-
- 10 (trimethylsilyl)propanoic acid, 2-amino-3-(dimethyl(trimethylsilylmethylsilyl)propanoic acid, 2-amino-2-phenylacetic acid, 2-amino-2-(3-chlorophenyl)acetic acid, 2-amino-2-(4-chlorophenyl)acetic acid, 2-amino-2-(3-fluorophenyl)acetic acid, 2-amino-2-(3-methylphenyl)acetic
- 15 acid, 2-amino-2-(4-fluorophenyl)acetic acid, 2-amino-2-(4-methylphenyl)acetic acid, 2-amino-2-(4-methoxyphenyl)acetic acid, 2-amino-2-(2-fluorophenyl)acetic acid, 2-amino-2-(2-methylphenyl)acetic acid, 2-amino-2-(4-chloromethylphenyl)acetic acid, 2-amino-2-(4-
- 20 hydroxymethylphenyl)acetic acid, 2-amino-2-[4-(methylthiomethyl)phenyl]acetic acid, 2-amino-2-(4-bromomethylphenyl)acetic acid, 2-amino-2-(4-(methoxymethyl)phenyl)acetic acid, 2-amino-2-(4-((N-benzylamino)methyl)phenyl)acetic acid, 2-amino-2-(4-
- 25 hydroxylphenyl)acetic acid, 2-amino-2-(3-hydroxylphenyl)acetic acid, 2-amino-2-(3-carboxyphenyl)acetic acid, 2-amino-2-(4-aminophenyl)acetic acid, 2-amino-2-(4-azidophenyl)acetic acid, 2-amino-2-(3-t-butyl-4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-difluoro-
- 30 4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-dihydroxyphenyl)acetic acid, 2-amino-2-(3-carboxy-4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-di-t-butyl-4-hydroxyphenyl)acetic acid, 2-amino-3-(2-methylphenyl)propanoic acid, 2-amino-3-(4-
- 35 ethylphenyl)propanoic acid, 2-amino-3-(4-phenylphenyl)propanoic acid, 2-amino-3-(4-benzylphenyl)propanoic acid, 2-amino-3-(3-fluorophenyl)propanoic acid, 2-amino-3-(4-methylphenyl)propanoic acid, 2-amino-3-(4-
- 40 fluorophenyl)propanoic acid, 2-amino-3-(4-chlorophenyl)propanoic acid, 2-amino-3-(2-

- 5 chlorophenyl)propanoic acid, 2-amino-3-(4-bromophenyl)propanoic acid, 2-amino-3-(2-bromophenyl)propanoic acid, 2-amino-3-(3-hydroxyphenyl)propanoic acid, 2-amino-3-(2-hydroxyphenyl)propanoic acid, 2-amino-3-(4-mercaptophenyl)propanoic acid, 2-amino-3-(3-trifluoromethylphenyl)propanoic acid, 2-amino-3-(3-hydroxyphenyl)propanoic acid, 2-amino-3-(4-hydroxyphenyl)propanoic acid, 2-amino-3-[4-(hydroxymethyl)phenyl]propanoic acid, 2-amino-3-[3-(hydroxymethyl)phenyl]propanoic acid, 2-amino-3-[3-(aminomethyl)phenyl]propanoic acid, 2-amino-3-(3-carboxyphenyl)propanoic acid, 2-amino-3-(4-nitrophenyl)propanoic acid, 2-amino-3-(4-aminophenyl)propanoic acid, 2-amino-3-(4-azidophenyl)propanoic acid, 2-amino-3-(4-cyanophenyl)propanoic acid, 2-amino-3-(4-acetophenyl)propanoic acid, 2-amino-3-(4-guanidinophenyl)propanoic acid, 2-amino-3-[4-(phenylazo)phenyl]propanoic acid, 2-amino-3-[4-(2-phenylethylenyl)phenyl]propanoic acid, 2-amino-3-(4-trialkylsilylphenyl)propanoic acid, 2-amino-3-(2,4-dimethylphenyl)propanoic acid, 2-amino-3-(2,3-dimethylphenyl)propanoic acid, 2-amino-3-(2,5-dimethylphenyl)propanoic acid, 2-amino-3-(3,5-dimethylphenyl)propanoic acid, 2-amino-3-(2,4,6-trimethylphenyl)propanoic acid, 2-amino-3-(3,4,5-trimethylphenyl)propanoic acid, 2-amino-3-(2,3,4,5,6-pentamethylphenyl)propanoic acid, 2-amino-3-(2,4,-difluorophenyl)propanoic acid, 2-amino-3-(3,4,-difluorophenyl)propanoic acid, 2-amino-3-(2,5,-difluorophenyl)propanoic acid, 2-amino-3-(2,6,-difluorophenyl)propanoic acid, 2-amino-3-(2,3,5,6-tetrafluorophenyl)propanoic acid, 2-amino-3-(3,5-dichloro-2,4,6-trifluorophenyl)propanoic acid, 2-amino-3-(2,3-difluorophenyl)propanoic acid, 2-amino-3-(2,3-bistrifluoromethylphenyl)propanoic acid, 2-amino-3-(2,4-

- 5 bistrifluoromethylphenyl)propanoic acid, 2-amino-3-(2-chloro-5-trifluoromethylphenyl)propanoic acid, 2-amino-3-(2,5-difluorophenyl)propanoic acid, 2-amino-3-(2,3,4,5,6-pentafluorophenyl)propanoic acid, 2-amino-3-(2,3-dibromophenyl)propanoic acid, 2-amino-3-(2,5-dibromophenyl)propanoic acid, 2-amino-3-(3,4-dibromophenyl)propanoic acid, 2-amino-3-(3,4,5-triiodophenyl)propanoic acid, 2-amino-3-(2,3-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,6-dihydroxyphenyl)propanoic acid, 2-amino-3-(3-bromo-5-methoxyphenyl)propanoic acid, 2-amino-3-(2,5-dimethoxyphenyl)propanoic acid, 2-amino-3-(2,5-dimethoxy-4-methylphenyl)propanoic acid, 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propanoic acid, 2-amino-3-(3-carboxy-4-hydroxyphenyl)propanoic acid, 2-amino-3-(3-carboxy-4-aminophenyl)propanoic acid, 2-amino-3-(2-hydroxy-5-nitrophenyl)propanoic acid, 2-amino-3-(2-ethoxy-5-nitrophenyl)propanoic acid, 2-amino-3-(3,4,5-trimethoxyphenyl)propanoic acid, 2-amino-3-(4-azido-2-nitrophenyl)propanoic acid, 2-amino-3-(2-hydroxy-5-nitrophenyl)propanoic acid, 2-amino-3-(2,4-bis-trimethylsilylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-di-t-butylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-benzylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-fluorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-2,3,5,6-tetrafluorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-dichlorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-iodophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-diiodophenyl)propanoic acid, 2-amino-3-(4-hydroxy-2-hydroxyphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-hydroxymethylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-2-hydroxy-6-methylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-carboxyphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-dinitrophenyl)propanoic acid, substituted
40 thyronines, 2-amino-3-(3,4-dihydroxy-2-chlorophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-

- 5 bromophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-fluorophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-nitrophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-methylphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-ethylphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-isopropylphenyl)propanoic acid, 2-amino-3-(2-t-butyl-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(3-fluoro-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(2-fluoro-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,5,6-trifluoro-3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,6-dibromo-3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(5,6-dibromo-3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,4,5-trihydroxyphenyl)propanoic acid, 2-amino-3-(2,3,4-trihydroxyphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-5-methoxyphenyl)propanoic acid, 2-amino-3-methyl-3-phenylpropanoic acid, 2-amino-3-ethyl-3-phenylpropanoic acid, 2-amino-3-isopropyl-3-phenylpropanoic acid, 2-amino-3-butyl-3-phenylpropanoic acid, 2-amino-3-benzyl-3-phenylpropanoic acid, 2-amino-3-phenylethyl-3-phenylpropanoic acid, 2-amino-3-(4-chlorophenyl)-3-phenylpropanoic acid, 2-amino-3-(4-methoxyphenyl)-3-phenylpropanoic acid, 2-amino-3,3-diphenylpropanoic acid, 2-amino-3-[4-(N,N-diethylamino)phenyl]heptanoic acid, 2-amino-3-[4-(N,N-diethylamino)phenyl]pentanoic acid, 2-amino-3-(3,4-dimethoxyphenyl)pentanoic acid, 2-amino-3-(3,4-dihydroxyphenyl)pentanoic acid, 2-amino-3-methyl-3-phenylbutanoic acid, 2-amino-3-ethyl-3-phenylpentanoic acid, 2-amino-3-methyl-3-phenylpentanoic acid, 2-amino-3,3-diphenylbutanoic acid, 2-amino-3-fluoro-3-phenylpropanoic acid, 2-amino-3-methylene-3-phenylpropanoic acid, 2-amino-3-methylmercapto-3-phenylpropanoic acid, 2-amino-4-methylmercapto-4-phenylbutanoic acid, 2-amino-4-(3,4-dihydroxyphenyl)butanoic acid, 2-amino-5-(4-methoxyphenyl)pentanoic acid, 2-amino-4-phenylbutanoic acid, 2-amino-5-phenylpentanoic acid, 2-amino-3,3-dimethyl-5-phenylpentanoic acid, 2-amino-4-phenyl-3-butenic acid, 2-amino-4-phenoxybutanoic acid, 2-amino-5-phenoxy-pentanoic

5 acid, 2-amino-2-(indanyl)acetic acid, 2-amino-2-(1-tetralyl)acetic acid, 2-amino-4,4-diphenylbutanoic acid, 2-amino-2-(2-naphthyl)acetic acid, 2-amino-3-(1-naphthyl)propanoic acid, 2-amino-3-(1-naphthyl)pentanoic acid, 2-amino-3-(2-naphthyl)propanoic acid, 2-amino-3-(1-chloro-2-naphthyl)propanoic acid, 2-amino-3-(1-bromo-2-naphthyl)propanoic acid, 2-amino-3-(4-hydroxy-1-naphthyl)propanoic acid, 2-amino-3-(4-methoxy-1-naphthyl)propanoic acid, 2-amino-3-(4-hydroxy-2-chloro-1-naphthyl)propanoic acid, 2-amino-3-(2-chloro-4-methoxy-1-naphthyl)propanoic acid, 2-amino-2-(2-anthryl)acetic acid, 2-amino-3-(9-anthryl)propanoic acid, 2-amino-3-(2-fluorenyl)propanoic acid, 2-amino-3-(4-fluorenyl)propanoic acid, 2-amino-3-(carboranyl)propanoic acid, 3-methylproline, 4-methylproline, 5-methylproline, 4,4-dimethylproline, 4-fluoroproline, 4,4-difluoroproline, 4-bromoproline, 4-chloroproline, 3,4-dehydroproline, 4-methylproline, 4-methyleneproline, 4-mercaptoproline, 4-(4-methoxybenzylmercapto)proline, 4-hydroxymethylproline, 3-hydroxyproline, 3-hydroxy-5-methylproline, 3,4-dihydroxyproline, 3-phenoxyproline, 3-carbamylalkylproline, 4-cyano-5-methyl-5-carboxyproline, 4,5-dicarboxyl-5-methylproline, 2-aziridinecarboxylic acid, 2-azetidinecarboxylic acid, 4-methyl-2-azetidinecarboxylic acid, pipecolic acid, 1,2,3,6-tetrahydropicolinic acid, 3,4-methyleneproline, 2,4-methyleneproline, 4-aminopipecolic acid, 5-hydroxypipecolic acid, 4,5-dihydroxypipecolic acid, 5,6-dihydroxy-2,3-dihydroindole-2-carboxylic acid, 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,3-oxazolidine-4-carboxylic acid, 1,2-oxazolidine-3-carboxylic acid, perhydro-1,4-thiazine-3-carboxylic acid, 2,2-dimethylthiazolidine-4-carboxylic acid, perhydro-1,3-thiazine-2-carboxylic acid, selenazolidine-4-carboxylic

- 5 acid, 2-phenylthiazolidine-4-carboxylic acid, 2-(4-carboxylicyl)thiazolidine-4-carboxylic acid, 1,2,3,4,4a,9a-hexahydro-beta-carboline-3-carboxylic acid, 2,3,3a,8a-tetrahydropyrrolo(2,3b)indole-2-carboxylic acid, 2-amino-3-(2-pyridyl)propanoic acid, 2-amino-3-(3-pyridyl)propanoic
- 10 acid, 2-amino-3-(4-pyridyl)propanoic acid, 2-amino-3-(2-bromo-3-pyridyl)propanoic acid, 2-amino-3-(2-bromo-4-pyridyl)propanoic acid, 2-amino-3-(2-bromo-5-pyridyl)propanoic acid, 2-amino-3-(2-bromo-6-pyridyl)propanoic acid, 2-amino-3-(2-chloro-3-pyridyl)propanoic acid, 2-amino-3-(2-chloro-4-pyridyl)propanoic acid, 2-amino-3-(2-chloro-5-pyridyl)propanoic acid, 2-amino-3-(2-chloro-6-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-3-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-4-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-5-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-6-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-3-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-4-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-5-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-6-pyridyl)propanoic acid, 2-amino-3-(5-hydroxy-2-pyridyl)propanoic acid, 2-amino-3-(5-hydroxy-6-iodo-2-pyridyl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxo-1,4-dihydro-1-pyridyl)propanoic acid, N-(5-carboxyl-5-aminopentyl)pyridinium chloride, 1,2,5-trimethyl-4-(2-amino-2-carboxy-1-hydroxyethyl)pyridinium chloride, 2-amino-2-(5-chloro-2-pyridyl)acetic acid, N-(3-amino-3-carboxypropyl)pyridinium chloride, 2-amino-3-(2-pyrryl)propanoic acid, 2-amino-3-(1-pyrryl)propanoic acid,
- 35 2-amino-4-(1-pyrryl)butanoic acid, 2-amino-5-(1-pyrryl)pentanoic acid, 2-amino-3-(5-imidazolyl)-3-methylpropanoic acid, 2-amino-3-(5-imidazolyl)-3-ethylpropanoic acid, 2-amino-3-hexyl-3-(5-imidazolyl)propanoic acid, 2-amino-3-hydroxy-3-(5-imidazolyl)propanoic acid, 2-amino-3-(4-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(4-methyl-5-
- 40

- 5 imidazolyl)propanoic acid, 2-amino-3-(2-methyl-5-imidazolyl)propanoic acid, 2-amino-3-(4-fluoro-5-imidazolyl)propanoic acid, 2-amino-3-(2-fluoro-5-imidazolyl)propanoic acid, 2-amino-3-(2-amino-5-imidazolyl)propanoic acid, 2-amino-3-(2-phenylaza-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-2-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-4-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-5-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(2-mercapto-5-imidazolyl)propanoic acid, 2-amino-4-(5-imidazolyl)butanoic acid, 2-amino-3-(1-imidazolyl)propanoic acid, 2-amino-3-(2-imidazolyl)propanoic acid, 2-amino-(1-pyrazolyl)propanoic acid, 2-amino-(3-pyrazolyl)propanoic acid, 2-amino-(3,5-dialkyl-4-pyrazolyl)propanoic acid, 2-amino-3-(3-amino-1,2,4-triazol-1-yl)propanoic acid, 2-amino-3-(tetrazol-5-yl)propanoic acid, 2-amino-4-(5-tetrazolyl)butanoic acid, 2-amino-3-(6-methyl-3-indolyl)propanoic acid, 2-amino-3-(4-fluoro-3-indolyl)propanoic acid, 2-amino-3-(5-fluoro-3-indolyl)propanoic acid, 2-amino-3-(6-fluoro-3-indolyl)propanoic acid, 2-amino-3-(4,5,6,7-tetrafluoro-3-indolyl)propanoic acid, 2-amino-3-(5-chloro-3-indolyl)propanoic acid, 2-amino-3-(6-chloro-3-indolyl)propanoic acid, 2-amino-3-(7-chloro-3-indolyl)propanoic acid, 2-amino-3-(5-bromo-3-indolyl)propanoic acid, 2-amino-3-(7-bromo-3-indolyl)propanoic acid, 2-amino-3-(2-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(5-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(7-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(2-alkylmercapto-3-indolyl)propanoic acid, 2-amino-3-(7-amino-3-indolyl)propanoic acid, 2-amino-3-(4-nitro-3-indolyl)propanoic acid, 2-amino-3-(7-nitro-3-indolyl)propanoic acid, 2-amino-3-(4-carboxy-3-indolyl)propanoic acid, 2-amino-3-(3-indolyl)butanoic acid, 2-amino-3-(2,3-dihydro-3-indolyl)propanoic acid, 2-amino-3-(2,3-dihydro-2-oxo-3-indolyl)propanoic acid, 2-amino-3-alkylmercapto-3-(3-indolyl)propanoic acid, 2-amino-3-(4-

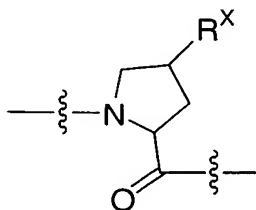
- 5 aza-3-indolyl)propanoic acid, 2-amino-3-(7-aza-3-indolyl)propanoic acid, 2-amino-3-(7-aza-6-chloro-4-methyl-3-indolyl)propanoic acid, 2-amino-3-(2,3-dihydrobenzofuran-3-yl)propanoic acid, 2-amino-3-(3-methyl-5-7-dialkylbenzofuran-2-yl)propanoic acid, 2-amino-3-
- 10 (benzothiophen-3-yl)propanoic acid, 2-amino-3-(5-hydroxybenzothiophen-3-yl)propanoic acid, 2-amino-3-eoenzoselenol-3yl)propanoic acid, 2-amino-3-quinolylpropanoic acid, 2-amino-3-(8-hydroxy-5-quinolyl)propanoic acid, 2-amino-2-(5,6,7,8-
- 15 tetrahydroquinol-5-yl)acetic acid, 2-amino-3-(3-coumarinyl)propanoic acid, 2-amino-2-(benzisoxazol-3-yl)acetic acid, 2-amino-2-(5-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(6-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(7-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-
- 20 (5-bromobenzisoxazol-3-yl)acetic acid, 2-amino-3-(benzimidazol-2-yl)propanoic acid, 2-amino-3-(5,6-dichlorobenzimidazol-2-yl)propanoic acid, 2-amino-3-(5,6-dimethylbenzimidazol-2-yl)propanoic acid, 2-amino-3-(4,5,6,7-hydrobenzirnidazol-2-yl)propanoic acid, 2-amino-2-
- 25 (benzimidazol-5-yl)acetic acid, 2-amino-2-(1,3-dihydro-2,2-dioxoisobenzothiophen-5-yl)acetic acid, 2-amino-2-(1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl)acetic acid, 2-amino-2-(2-oxobenzimidazol-5-yl)acetic acid, 2-amino-3-(4-hydroxybenzothiazol-6-yl)propanoic acid, 2-amino-3-
- 30 (benzoxazol-2-yl)propanoic acid, 2-amino-3-(benzothiazol-2-yl)propanoic acid, 2-amino-3-(9-adeninyl)propanoic acid, 2-amino-2-(6-chloro-9-purinyl)acetic acid, 2-amino-2-(6-amino-9-purinyl)acetic acid, 2-amino-3-(6-purinyl)propanoic acid, 2-amino-3-(8-theobrominyl)propanoic acid, 2-amino-2-
- 35 (1-uracilyl)acetic acid, 2-amino-2-(1-cytosinyl)acetic acid, 2-amino-3-(1-uracilyl)propanoic acid, 2-amino-3-(1-cytosinyl)propanoic acid, 2-amino-4-(1-pyrimidinyl)butanoic acid, 2-amino-4-(4-amino-1-pyrimidinyl)butanoic acid, 2-amino-4-(4-hydroxy-1-pyrimidinyl)butanoic acid, 2-amino-5-
- 40 (1-pyrimidinyl)pentanoic acid, 2-amino-5-(4-amino-1-pyrimidinyl)pentanoic acid, 2-amino-5-(4-hydroxy-1-

5 pyrimidinyl)pentanoic acid, 2-amino-3-(5-pyrimidinyl)propanoic acid, 2-amino-3-(6-uracilyl)propanoic acid, 2-amino-3-(2-pyrimidinyl)propanoic acid, 2-amino-3-(6-amino-4-chloro-2-pyrimidinyl)propanoic acid, 2-amino-3-(4-hydroxy-2-pyrimidinyl)propanoic acid, 2-amino-3-(2-amino-4-pyrimidinyl)propanoic acid, 2-amino-3-(4,5-dihydroxypyrimidin-2-yl)propanoic acid, 2-amino-3-(2-thiouracil-6-yl)propanoic acid, 2-amino-2-(5-alkyl-2-tetrahydrofuryl)acetic acid, 2-amino-2-(5-methyl-2,5-dihydro-2-furyl)acetic acid, 2-amino-2-(5-alkyl-2-furyl)acetic acid, 2-amino-2-(2-furyl)acetic acid, 2-amino-2-(3-hydroxy-5-methyl-4-isoxazolyl)acetic acid, 2-amino-3-(4-bromo-3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-3-(4-methyl-3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-3-(3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-2-(3-chloro-D2 -isoxazolin-5-yl)acetic acid, 2-amino-2-(3-oxo-5-isoxazolidinyl)acetic acid, 2-amino-3-(3,5-dioxo-1,2,4-oxadiazolin-2-yl)propanoic acid, 2-amino-3-(3-phenyl-5-isoxazolyl)propanoic acid, 2-amino-3-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]propanoic acid, 2-amino-3-(2-thienyl)propanoic acid, 2-amino-2-(2-furyl)acetic acid, 2-amino-2-(2-thienyl)acetic acid, 2-amino-2-(2-thiazolyl)acetic acid, 2-amino-3-(2-thiazolyl)propanoic acid, 2-amino-4-(4-carboxy-2-thiazolyl)butanoic acid, 2-amino-3-(4-thiazolyl)propanoic acid, 2-amino-3-(2-selenolyl)propanoic acid, 2-amino-3-(2-amino-4-selenolyl)propanoic acid, and 2-amino-3-(beta-ribofuranosyl)propanoic acid.

"Amino acid residue" also refers to various amino acids where sidechain functional groups are modified with appropriate protecting groups known to those skilled in the art. "The Peptides", Vol 3, 3-88 (1981) discloses numerous suitable protecting groups and is incorporated herein by reference for that purpose. Examples of amino acids where sidechain functional groups are modified with appropriate protecting groups include, but are not limited to, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu),

5 Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), and Thr(OBzl); wherein OMe is methoxy, O^tBu is tert-butoxy, and OBzl is benzyloxy.

A preferred list of "amino acid residue" in the present invention includes, but is not limited to, Ala,
 10 Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Leu, Lys, Met, Orn, Phe, Pro, Sar, Ser, Thr, Trp, Tyr, Val, Abu, Alg, Ape, Cha, Cpa, Cpg, Dfb, Dpa, Gla, Irg, HomoLys, Phe(4-fluoro), Tpa, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu), Hyp(O^tBu), Thr(O^tBu), Asp(OBzl),
 15 Glu(OBzl), Hyp(OBzl), Thr(OBzl), cyclohexylglycine, cyclohexylalanine, cyclopropylglycine, t-butylglycine, phenylglycine, 3,3-diphenylalanine and

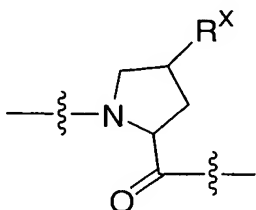


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A preferred scope of substituent A is A²-A³, A²-A³-A⁴, A²-A³-A⁴-A⁵, A²-A³-A⁴-A⁵-A⁶.

A preferred scope of substituent A² is Pro, Leu, Asp, Abu, Val, cyclohexylalanine and

25



A preferred scope of substituent A³ is Val, Glu, Ile, Thr, cyclohexylglycine, and cyclohexylalanine.

A preferred scope of substituent A⁴ is Val, Ile, Leu,
 30 cyclohexylglycine, cyclopropylglycine, t-butylglycine, phenylglycine, and 3,3-diphenylalanine.

5 A preferred scope of substituent A⁵ is (D or L stereochemistry) Asp, Glu, Val, Ile, t-butylglycine, and Gla.

 A preferred scope of substituent A⁶ is Asp and Glu.

10 As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; for example, "C₁-C₆ alkyl" denotes alkyl having 1 to 6 carbon atoms. Examples of alkyl include, but
15 are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

 "Alkenyl" or "alkenylene" is intended to include
20 hydrocarbon chains of either a straight or branched configuration having the specified number of carbon atoms and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain. Examples of alkenyl include, but are not limited to, ethenyl, 1-
25 propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

 "Alkynyl" or "alkynylene" is intended to include
30 hydrocarbon chains of either a straight or branched configuration and one or more carbon-carbon triple bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

35 "Cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. For example, "C₃-C₆ cycloalkyl" denotes such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

 "Alkoxy" or "alkyloxy" represents an alkyl group as
40 defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy

5 include, but are not limited to, methoxy, ethoxy,
n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy,
n-pentoxy, and s-pentoxy. Similarly, "alkylthio" or
"thioalkoxy" represents an alkyl group as defined above
with the indicated number of carbon atoms attached through
10 a sulphur bridge.

"Halo" or "halogen" as used herein refers to fluoro,
chloro, bromo, and iodo; and "counterion" is used to
represent a small, negatively charged species such as
chloride, bromide, hydroxide, acetate, sulfate, and the
15 like.

"Haloalkyl" is intended to include both branched and
straight-chain saturated aliphatic hydrocarbon groups
having the specified number of carbon atoms, substituted
with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3
20 and $w = 1$ to $(2v+1)$). Examples of haloalkyl include, but
are not limited to, trifluoromethyl, trichloromethyl,
pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl,
heptafluoropropyl, and heptachloropropyl. Examples of
haloalkyl also include "fluoroalkyl" which is intended to
25 include both branched and straight-chain saturated
aliphatic hydrocarbon groups having the specified number of
carbon atoms, substituted with 1 or more fluorine atoms.

As used herein, "carbocycle", "carbocyclic ring",
"carbocyclic group", or "carbocyclic ring system" is
30 intended to mean any stable 3- to 7-membered monocyclic or
bicyclic or 7- to 13-membered bicyclic or tricyclic, any of
which may be saturated, partially unsaturated, or aromatic.
Examples of such carbocycles include, but are not limited
to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
35 cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane,
[4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin),
[2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl,
adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle", "heterocyclic
40 group", "heterocyclic ring" "heterocyclic ring system" or
"Het" is intended to mean a stable 5- to 7- membered

5 monocyclic or bicyclic or 7- to 14-membered bicyclic
heterocyclic ring which is saturated, partially unsaturated
or unsaturated (aromatic), and which consists of carbon
atoms and 1, 2, 3 or 4 heteroatoms independently selected
10 bicyclic group in which any of the above-defined
heterocyclic rings is fused to a benzene ring. The
nitrogen and sulfur heteroatoms may optionally be oxidized.
The heterocyclic ring may be attached to its pendant group
at any heteroatom or carbon atom which results in a stable
15 structure. The heterocyclic rings described herein may be
substituted on carbon or on a nitrogen atom if the
resulting compound is stable. If specifically noted, a
nitrogen in the heterocycle may optionally be quaternized.
It is preferred that when the total number of S and O atoms
20 in the heterocycle exceeds 1, then these heteroatoms are
not adjacent to one another. It is preferred that the
total number of S and O atoms in the heterocycle is not
more than 1.

Examples of heterocycles include, but are not limited
25 to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl,
2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole,
4H-quinolizinyll, 6H-1,2,5-thiadiazinyl, acridinyl,
azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl,
benzothiophenyl, benzoxazolyl, benzoxazolinyl,
30 benzthiazolyl, benztriazolyl, benztetrazolyl,
benzisoxazolyl, benzisothiazolyl, benzimidazalonyl,
benzo[1,3]dioxol-yl, 2,3-dihydro-benzo[1,4]dioxin-yl,
carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl,
chromenyl, cinnolinyl, decahydroquinolinyl,
35 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran,
furanyl, furazanyl, imidazolidinyl, imidazolinyl,
imidazolyl, imidazolopyridinyl, 1H-indazolyl, indolenyl,
indolinyl, indolizinyll, indolyl, isatinoyl,
isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl,
40 isoindolyl, isoquinolinyl, isothiazolyl,
isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl,

5 morpholinyl, naphthyridinyl, octahydroisoquinolinyl,
oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,
1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl,
oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl,
oxindolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl,
10 phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,
phthalazinyl, piperazinyl, piperidinyl, pteridinyl,
piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl,
pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl,
pyrazolyl, pyridazinyl, pyridoaxazole, pyridoimidazole,
15 pyrimidopyrimidin-yl, pyridothiazole, pyridinyl, pyridyl,
pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl,
quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl,
quinuclidinyl, carbolinyl, tetrahydrofuranyl,
tetrahydroisoquinolinyl, tetrahydroquinolinyl,
20 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl,
1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,
thianthrenyl, thiazolyl, thiazolopyridinyl, thienyl,
thienothiazolyl, thienooxazolyl, thienoimidazolyl,
thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
25 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred
5-10 membered heterocycles include, but are not limited to,
pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,
pyrazinyl, piperazinyl, imidazolyl, indolyl,
benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl,
30 benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl,
benzthiazolyl, benzisothiazolyl, isatinoyl,
isoxazolopyridinyl, isothiazolopyridinyl,
thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl,
and pyrazolopyridinyl. Preferred 5 to 6 membered
35 heterocycles include, but are not limited to, pyridinyl,
furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl,
piperazinyl, imidazolyl, and oxazolidinyl. Also included
are fused ring and spiro compounds containing, for example,
the above heterocycles.

5 The term "Het-(lower alkyl)-" as used herein, means a heterocyclic ring as defined above linked through a chain or branched C₁-C₆ alkyl group.

 As used herein, the term "aryl", or aromatic residue, is intended to mean an aromatic moiety containing the
10 specified number of carbon atoms, such as phenyl and naphthyl.

 "NH₂-blocking group" as used herein, refers to various acyl, thioacyl, alkyl, sulfonyl, phosphoryl, and phosphinyl groups comprised of 1 to 20 carbon atoms. Substitutes on
15 these groups maybe either alkyl, aryl, alkylaryl which may contain the heteroatoms, O, S, and N as a substituent or in-chain component. A number of NH₂-blocking groups are recognized by those skilled in the art of organic synthesis. By definition, an NH₂-blocking group may be
20 removable or may remain permanently bound to the NH₂. Examples of suitable groups include formyl, acetyl, benzoyl, trifluoroacetyl, and methoxysuccinyl; aromatic urethane protecting groups, such as, benzyloxycarbonyl; and aliphatic urethane protecting groups, such as t-
25 butoxycarbonyl or adamantyloxycarbonyl. Gross and Meinhoffer, eds., The Peptides, Vol 3; 3-88 (1981), Academic Press, New York, and Greene and Wuts Protective Groups in Organic Synthesis, 315-405 (1991), J. Wiley and Sons, Inc., New York disclose numerous suitable amine
30 protecting groups and they are incorporated herein by reference for that purpose. Amine protecting groups may include, but are not limited to the following: 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothio-xanthyl)]methylo xycarbonyl; 2-
35 trimethylsilylethyloxycarbonyl; 2-phenylethyloxycarbonyl; 1,1-dimethyl-2,2-dibromoethyloxycarbonyl; 1-methyl-1-(4-biphenyl)ethyloxycarbonyl; benzyloxycarbonyl; p-nitrobenzyloxycarbonyl; 2-(p-toluenesulfonyl)ethyloxycarbonyl; m-chloro-p-
40 acyloxybenzyloxycarbonyl; 5-benzyisoxazolylmethyloxycarbonyl; p-

5 (dihydroxyboryl)benzyloxycarbonyl; m-nitrophenyloxycarbonyl; o-nitrobenzyloxycarbonyl; 3,5-dimethoxybenzyloxycarbonyl; 3,4-dimethoxy-6-nitrobenzyloxycarbonyl; N'-p-toluenesulfonylaminocarbonyl; t-amyloxycarbonyl; p-decyloxybenzyloxycarbonyl;
10 diisopropylmethyloxycarbonyl; 2,2-dimethoxycarbonylvinyloxycarbonyl; di(2-pyridyl)methyloxycarbonyl; 2-furanylmethyloxycarbonyl; phthalimide; dithiasuccinimide; 2,5-dimethylpyrrole; benzyl; 5-dibenzylsuberyl; triphenylmethyl; benzylidene;
15 diphenylmethylene; or methanesulfonamide.

As used herein, "cyclic boronic ester" is intended to mean a stable cyclic boronic moiety of general formula $-B(OR)(OR)$ wherein the two R substituents taken together contain from 2 to 20 carbon atoms, and optionally, 1, 2, or
20 3 heteroatoms which can be N, S, or O. Cyclic boronic esters are well known in the art. Examples of cyclic boronic ester include, but are not limited to, pinanediol boronic ester, pinacol boronic ester, 1,2-ethanediol boronic ester, 1,3-propanediol boronic ester, 1,2-propanediol boronic ester, 2,3-butanediol boronic ester,
25 1,2-diisopropylethanediol boronic ester, 5,6-decanediol boronic ester, 1,2-dicyclohexylethanediol boronic ester, diethanolamine boronic ester, and 1,2-diphenyl-1,2-ethanediol boronic ester.

30 As used herein, "cyclic boronic amide" is intended to mean a stable cyclic boronic amide moiety of general formula $-B(NR)(NR)$ wherein the two R substituents taken together contain from 2 to 20 carbon atoms, and optionally, 1, 2, or 3 heteroatoms which can be N, S, or O. Examples
35 of cyclic boronic amide include, but are not limited to, 1,3-diaminopropane boronic amide and ethylenediamine boronic amide.

As used herein, "cyclic boronic amide-ester" is intended to mean a stable cyclic boronic amide-ester moiety
40 of general formula $-B(OR)(NR)$ wherein the two R substituents taken together contain from 2 to 20 carbon

5 atoms, and optionally, 1, 2, or 3 heteroatoms which can be N, S, or O. Examples of cyclic boronic amide include, but are not limited to, 3-amino-1-propanol boronic amide-ester and ethanolamine boronic amide-ester.

The phrase "pharmaceutically acceptable" is employed
10 herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response,
15 or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts
20 thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the
25 conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic,
30 sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic,
35 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which
40 contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting

5 the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists
10 of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p.1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently
15 bonded carriers which release the active parent drug according to Formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula (I) are prepared by modifying functional groups present in the compound in such a way
20 that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of Formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of Formula (I) is administered to a
25 mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula (I), and the like.

30 "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

35 The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in an animal which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder or condition, i.e.,
40 arresting its development; and (iii) relieving the disease,

- 5 disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

SYNTHESIS

10 The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those
15 skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

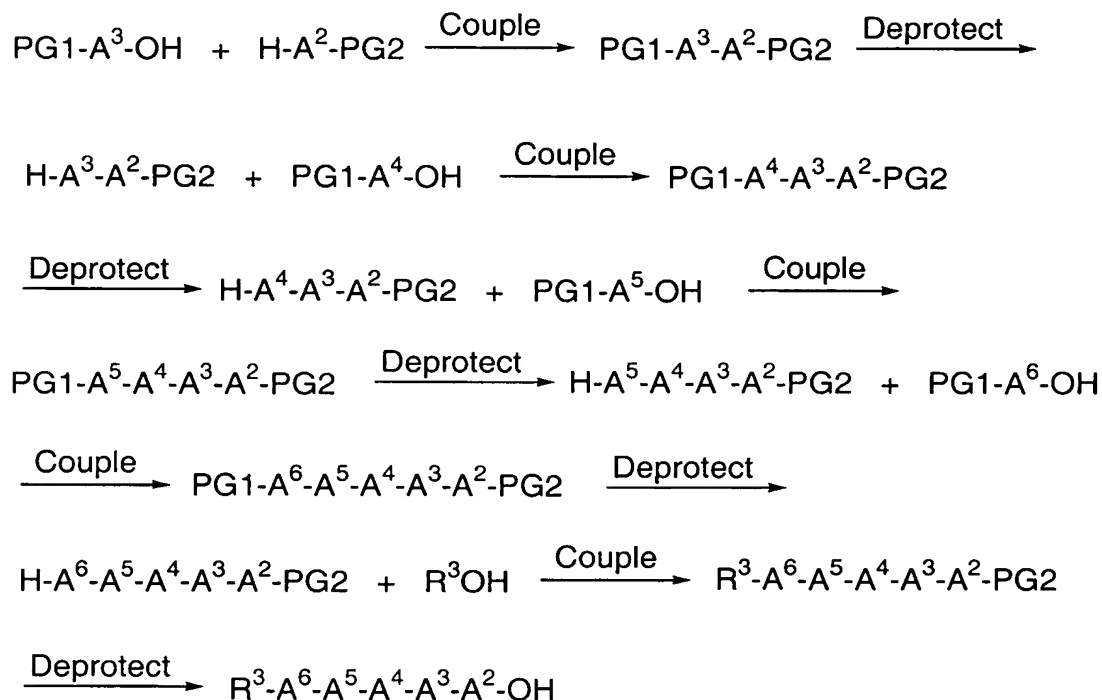
20 The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below,
25 it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be
30 readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are
35 compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

5 Synthesis of A⁶-A⁵-A⁴-A³-A² peptide fragments

The A⁶-A⁵-A⁴-A³-A² fragments of the compounds of the present invention were synthesized according to the process as illustrated in Scheme 1 (wherein PG1 is an amino protecting group and PG2 is a carboxyl protecting group):

10

Scheme 1



15 Briefly, the A², A³, and optionally A⁴, A⁵, and A⁶ amino acids can be linked by well known peptide coupling techniques. The A², A³, A⁴, A⁵ and A⁶ moieties may be linked together in any order as long as the final compound corresponds to peptides of Formula (I). For example, A⁶ can be linked to A⁵ to give A⁶-A⁵ that is linked to A⁴-A³-A²; or A⁶ linked to A⁵-A⁴-A³ then linked to an appropriately C-terminal protected A². Consequently, Scheme 1 enables one skilled in the art to make peptides wherein A is A³-A², A⁴-A³-A², A⁵-A⁴-A³-A², or A⁶-A⁵-A⁴-A³-A².

20

5 Generally, peptides are elongated by deprotecting the
α-amino group of the N-terminal residue and coupling to the
unprotected carboxyl group of the next suitably N-protected
amino acid through a peptide linkage using the methods
described. This deprotection and coupling procedure is
10 repeated until the desired sequence is obtained. This
coupling can be performed with the constituent amino acids
in stepwise fashion, as depicted in Scheme 1, or by
condensation of fragments (two or several amino acids), or
combination of both processes, or by solid phase peptide
15 synthesis according to the method originally described in
Merrifield, J. Am. Chem. Soc., (1963), 85, 2149-2154, the
disclosure of which is hereby incorporated by reference.
Coupling between two amino acids, an amino acid and a
peptide, or two peptide fragments can be carried out using
20 standard coupling procedures such as the azide method,
mixed carbonic-carboxylic acid anhydride (isobutyl
chloroformate) method, carbodiimide (1,3-
dicyclohexylcarbodiimide, diisopropylcarbodiimide, or
water-soluble carbodiimide) method, active ester (p-
25 nitrophenyl ester, N-hydroxysuccinic imido ester) method,
Woodward reagent K-method, carbonyldiimidazole method,
phosphorus reagents or oxidation-reduction methods. Some of
these methods (especially the carbodiimide method) can be
enhanced by adding 1-hydroxybenzotriazole (HOBt) or 1-
30 hydroxy-7-azabenzotriazole (HOAt). These coupling reactions
can be performed in either solution (liquid phase) or on
solid phase. More explicitly, the coupling step involves
the dehydrative coupling of a free carboxyl of one reactant
with the free amino group of the other reactant in the
35 presence of a coupling agent to form a linking amide bond.
Description of such coupling agents are found in general
textbooks on peptide chemistry, for example, M. Bodanszky,
"Peptide Chemistry", 2nd rev ed., Springer-Verlag, Berlin,
Germany, (1993). Examples of suitable coupling agents are
40 N,N'-1,3-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole
in the presence of N,N' 1,3-dicyclohexylcarbodiimide or N-

5 ethyl-N'-[(3 dimethylamino)propyl]carbodiimide. A very practical and useful coupling agent is the commercially available (benzotriazol-1-yloxy)tris (dimethylamino)phosphonium hexafluorophosphate, either by itself or in the presence of 1-hydroxybenzotriazole.

10 Another very practical and useful coupling agent is commercially available 2-(1H-benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium tetrafluoroborate. Still another very practical and useful coupling agent is commercially available 2-(7-azabenzotriazol-1-yl) N,N,N',N'-

15 tetramethyluronium hexafluorophosphate. The coupling reaction is conducted in an inert solvent, e.g. dichloromethane, acetonitrile or dimethylformamide. An excess of a tertiary amine, e.g. diisopropylethylamine, N-methylmorpholine or N-methylpyrrolidine, or sodium

20 bicarbonate is added to maintain the reaction mixture at a pH of about 8. The reaction temperature usually ranges between 0 °C and 50 °C and the reaction time usually ranges between 15 min and 24 h. When a solid phase synthetic approach is employed, the C-terminal carboxylic acid is

25 attached to an insoluble carrier (usually polystyrene). These insoluble carriers contain a group that will react with the carboxylic group to form a bond that is stable to the elongation conditions but readily cleaved later. Examples of which are: chloro- or bromomethyl resin,

30 hydroxymethyl resin, and aminomethyl resin. Many of these resins are commercially available with the desired C-terminal amino acid already incorporated. In addition to the foregoing, other methods of peptide synthesis are described in Stewart and Young, "Solid Phase Peptide

35 Synthesis", 2 nd ed., Pierce Chemical Co., Rockford, IL (1984); Gross, Meienhofer, Udenfriend, Eds., "The Peptides: Analysis, Synthesis, Biology", Vol. 1, 2, 3, 5, and 9, Academic Press, New-York, (1980-1987); Bodansky et al., "The Practice of Peptide Synthesis" Springer-Verlag, New-

40 York (1984), the disclosures of which are hereby incorporated by reference. The functional groups of the

5 constituent amino acids generally must be protected during
the coupling reactions to avoid formation of undesired
bonds. The is protecting groups that can be used are listed
in Greene, "Protective Groups in Organic Chemistry", John
Wiley & Sons, New York (1981) and "The Peptides: Analysis,
10 Synthesis, Biology", Vol. 3, Academic Press, New York
(1981), the disclosures of which are hereby incorporated by
reference. The α -carboxyl group of the C-terminal residue
is usually protected as an ester (PG2) that can be cleaved
to give the carboxylic acid. Protecting groups that can be
15 used include: 1) alkyl esters such as methyl, ethyl,
trimethylsilylethyl and t-butyl, 2) aralkyl esters such as
benzyl and substituted benzyl, or 3) esters that can be
cleaved by mild base treatment or mild reductive means such
as trichloroethyl and phenacyl esters. The α -amino group
20 of each amino acid to be coupled to the growing peptide
chain must be protected (PG1). Any protecting group known
in the art can be used. Examples of such groups include:
1) acyl groups such as formyl, trifluoroacetyl, phthalyl,
and p-toluenesulfonyl; 2) aromatic carbamate groups such as
25 benzyloxycarbonyl (Cbz or Z) and substituted
benzyloxycarbonyls, and 9-fluorenylmethyloxycarbonyl
(Fmoc); 3) aliphatic carbamate groups such as tert-
butyloxycarbonyl (Boc), ethoxycarbonyl,
diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic
30 alkyl carbamate groups such as cyclopentyloxycarbonyl and
adamantyloxycarbonyl; 5) alkyl groups such as
triphenylmethyl and benzyl; 6) trialkylsilyl such as
trimethylsilyl; and 7) thiol containing groups such as
phenylthiocarbonyl and dithiasuccinoyl. The preferred α -
35 amino protecting group is either Boc or Fmoc. Many amino
acid derivatives suitably protected for peptide synthesis
are commercially available. The α -amino protecting group of
the newly added amino acid residue is cleaved prior to the
coupling of the next amino acid. When the Boc group is
40 used, the methods of choice are trifluoroacetic acid, neat

5 or in dichloromethane, or HCl in dioxane or in ethyl
acetate. The resulting ammonium salt is then neutralized
either prior to the coupling or in situ with basic
solutions such as aqueous buffers, or tertiary amines in
dichloromethane or acetonitrile or dimethylformamide. When
10 the Fmoc group is used, the reagents of choice are
piperidine or substituted piperidine in dimethylformamide,
but any secondary amine can be used. The deprotection is
carried out at a temperature between 0 °C and room
temperature (RT). Any of the amino acids having side chain
15 functionalities must be protected during the preparation of
the peptide using any of the above described groups. Those
skilled in the art will appreciate that the selection and
use of appropriate protecting groups for these side chain
functionalities depend upon the amino acid and presence of
20 other protecting groups in the peptide. The selection of
such protecting groups is important in that the group must
not be removed during the deprotection and coupling of the
 α -amino group. For example, when Boc is used as the α -
amino protecting group, *p*-toluenesulfonyl (tosyl) is
25 suitable to protect the amino side chain of amino acids
such as Lys and Arg; acetamidomethyl, benzyl (Bn), or *t*-
butylsulfonyl moieties can be used to protect the sulfide
containing side chain of cysteine; benzyl (Bn) ethers can
be used to protect the hydroxy containing side chains of
30 serine, threonine or hydroxyproline; and benzyl esters can
be used to protect the carboxy containing side chains of
aspartic acid and glutamic acid. When Fmoc is chosen for
the α -amine protection, usually *tert*-butyl based protecting
groups are acceptable. For instance, Boc can be used for
35 lysine and arginine, *tert*-butyl ether for serine, threonine
and hydroxyproline, and *tert*-butyl ester for aspartic acid
and glutamic acid. Triphenylmethyl (Trityl) moiety can be
used to protect the sulfide containing side chain of
cysteine. Once the elongation of the peptide is completed,
40 all of the protecting groups are removed. When a liquid
phase synthesis is used, the protecting groups are removed

5 in whatever manner is dictated by the choice of protecting
groups. These procedures are well known to those skilled in
the art. When a solid phase synthesis is used, the peptide
is cleaved from the resin simultaneously with the removal
of the protecting groups. When the Boc protection method is
10 used in the synthesis, treatment with anhydrous HF
containing additives such as dimethyl sulfide, anisole,
thioanisole, or *p*-cresol at 0°C is the preferred method for
cleaving the peptide from the resin. The cleavage of the
peptide can also be accomplished by other acid reagents
15 such as trifluoromethanesulfonic acid/ trifluoroacetic acid
mixtures. If the Fmoc protection method is used, the N-
terminal Fmoc group is cleaved with reagents described
earlier. The other protecting groups and the peptide are
cleaved from the resin using solution of trifluoroacetic
20 acid and various additives such as anisole, etc.

Synthesis of capping group R³ and A⁶, A⁵, A⁴, A³ and A²
moieties

Different capping groups R³ are introduced to a
25 protected peptide segment containing a free amino terminus
with an appropriate acyl chloride, sulphonyl chloride, or
isocyanate that is either available commercially or can be
synthesized from methods known in the art. Different A² to
A⁶ amino acids are available commercially or their
30 synthesis is well known in the art. For instance, amino
acids may be synthesized in racemic form using the Strecker
synthesis or amidomalonate synthesis. In addition, the
Myers pseudoephedrine glycinamide alkylation method (Myers,
A. G.; Gleason, J. L.; Yoon, T; Kung, D. W.. *J. Am. Chem.*
35 *Soc.* **1997**, 119, 656-673) and the Evans electrophilic
azidation (Evans, D. A.; Britton, T. C.; Ellman, J. A.;
Dorow, R. L. *J. Am. Chem. Soc.* **1990**, 112, 4011) may be used
to prepare unnatural amino acids in enantiomerically pure
form. Introduction and manipulation of appropriate
40 protecting groups is well known in the art. Synthesis of
substituted prolines are well known in the art. Extensive

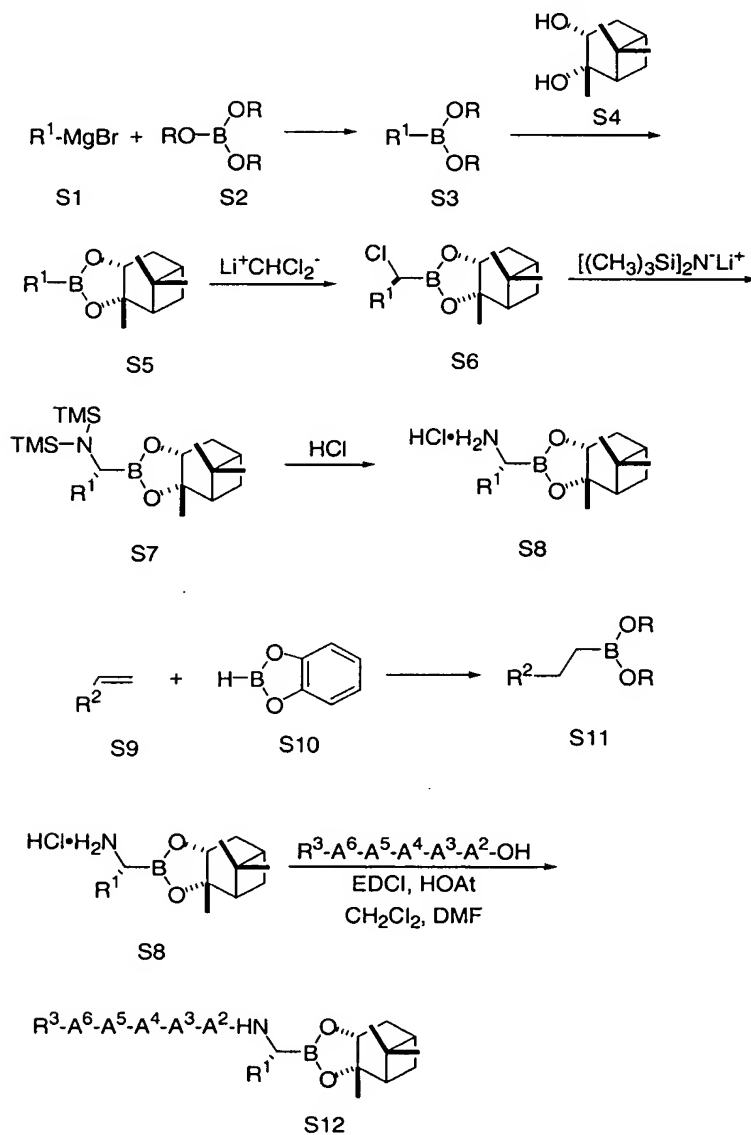
- 5 disclosure of substituted prolines can be found in WO
00/09543 and WO 00/09558 (Llinas-Brunet et al.).

Synthesis of P1 (-NR²-CHR¹-W) moiety and coupling to
Peptidyl Fragments

- 10 The P1 residue in the claimed compounds may contain a
boronic ester or acid (W = BY¹Y², an α -ketoamide (W =
COCONHQ), or other electrophilic carbonyl derivative known

Scheme 2

15

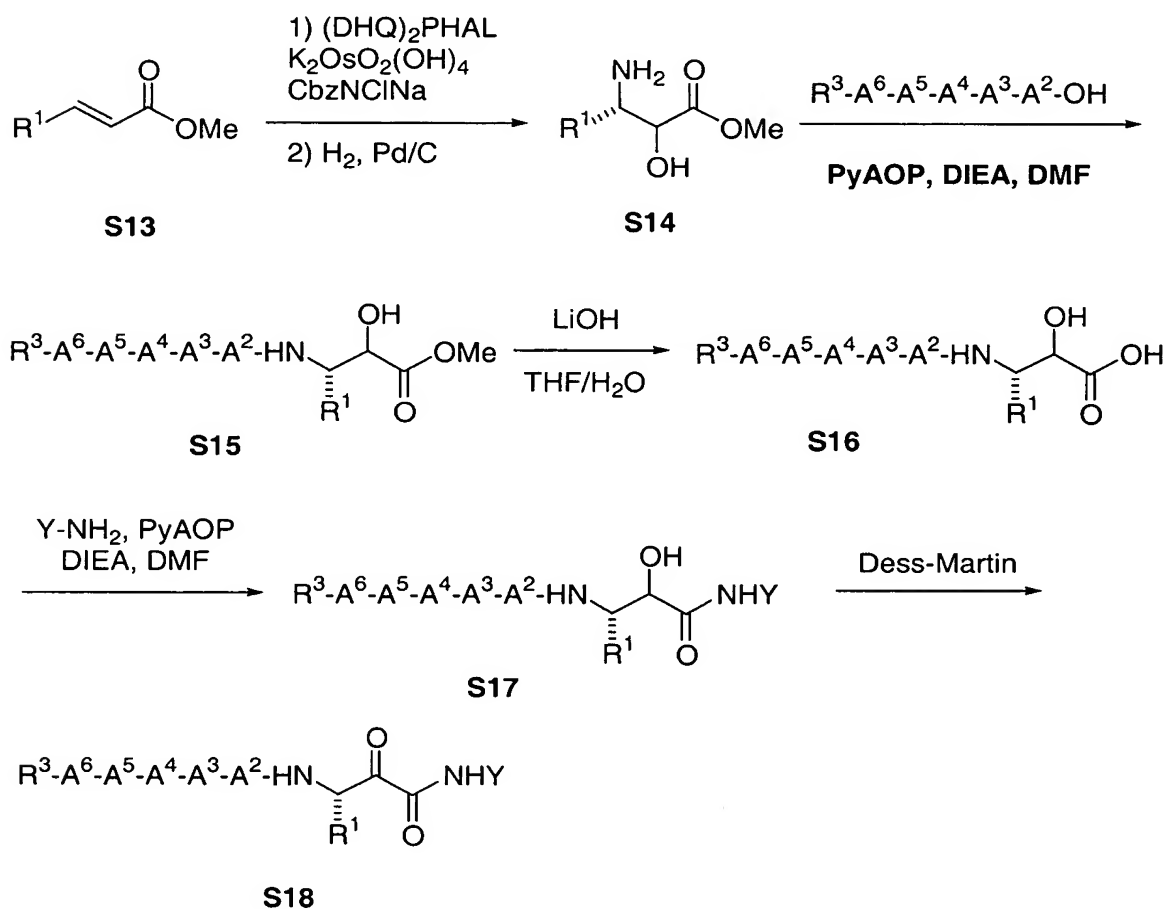


5 to one skilled in the art (Edwards, P. D.; Bernstein, P. R. *Medicinal Res. Reviews* **1994**, 14, 127-194, and references cited therein). Scheme 2 shows the synthetic route to α -amino boronic esters **S8** and their peptidyl derivatives. Grignard reagent **S1** is reacted with a trialkyl borate ester
10 **S2**, providing boronate **S3**. Transesterification with (+)-pinanediol **S4** affords the cyclic ester **S5**. This ester ultimately yields enantiomerically pure **S8** with L-configuration. Substitution of pinacol for pinanediol yields racemic product. Homologation of **S5** with the anion
15 of dichloromethane gives the α -chloro boronic ester **S6** (Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, 2, 1529-1535). Displacement of chloride by lithium bis(trimethylsilyl)amide gives silyl amine **S7**, which is converted to the amine hydrochloride **S8** with anhydrous HCl
20 (Matteson, D. S., Sadhu, K. M. *Organometallics* **1984**, 3, 1284-1288). An alternative route to boronate **S3** involves hydroboration of an olefin **S9** with catecholborane **S10** (Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, 97, 5249-5255), providing boronate **S11**, which may be converted
25 to **S8** by the same synthetic sequence as described above for **S3**. Compound **S8** is coupled to a peptide fragment using, for instance, EDCI/HOAt to generate peptide boronic ester **S12**. In some cases, a final step may be required to remove side chain protecting groups on the peptide. (For a general
30 reference to synthesis of peptide boronic esters, see: Kettner, C.; Forsyth, T. *Houben-Weyl Methods of Organic Chemistry* **2000**, in press.)

α -Ketoamides and other electrophilic ketone derivatives are generally introduced in the hydroxy form
35 and oxidized to the active ketone form in the final synthetic step. Scheme 3 illustrates the synthesis of peptidyl α -ketoamides. Other electrophilic ketone derivatives may be prepared analogously (Edwards, P. D.; Bernstein, P. R. *Medicinal Res. Reviews* **1994**, 14, 127-194,
40 and references cited therein). R¹ substituted acrylate

- 5 ester **S13** is aminohydroxylated and subsequently deprotected to give amino alcohol **S14**. The amino alcohol is coupled to a peptide fragment to give **S15**. Saponification with LiOH affords acid **S16**, which is coupled to an amine Y-NH₂, to give hydroxy amide **S17**. Oxidation with Dess-Martin
 10 periodinane affords the peptidyl α-keto amide **S18**.

Scheme 3



Examples

- Abbreviations used in the examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "rt" for room temperature, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "M" for molar, "mmol" for millimole or

5 millimoles, "min" for minute or minutes, "h" for hour or
hours, "MS" for mass spectrometry, "NMR" for nuclear
magnetic resonance spectroscopy, "¹H" for proton, "HPLC"
for high pressure liquid chromatography, "tlc" for thin
layer chromatography, "v/v" for volume to volume ratio,
10 "atm" for atmosphere, "α", "β", "R", and "S" are
stereochemical designations familiar to one skilled in the
art.

Example 1

15 Boc-Asp(O-tBu)-Glu(O-tBu)-Val-Val-Pro-OH

(1a) N-methylmorpholine (5.5 mL, 50 mmol) and 1,3-
dicyclohexylcarbodiimide (10 g, 48 mmol) were added
portionwise to a solution of L-proline benzyl ester
20 hydrochloride (12.5 g, 52 mmol), Boc-L-valine (10.9 g, 50
mmol) and 1-hydroxybenzotriazole (7.01 g, 52 mmol) in
chloroform (100 mL) at 0 °C. The reaction mixture was
allowed to slowly warm to room temperature overnight. The
crude mixture was filtered, extracted with 5% sodium
25 bicarbonate (2 x), 0.2 M hydrochloric acid (2 x) and brine,
dried (MgSO₄) and concentrated under reduced pressure. The
residual oil was purified by chromatography on silica gel
(10 to 30% ethyl acetate in hexane) to afford 1a as a white
solid (16.4 g, 84%). MS found: (M+H)⁺ = 405.

30 (1b) The Boc protected dipeptide 1a (10.5 g, 26 mmol) was
added to a solution of hydrogen chloride in 1,4-dioxane (50
mL, 4 M solution) at 0 °C. After 30 min, additional
hydrogen chloride in 1,4-dioxane (20 mL) was added and the
35 reaction mixture was stirred for 1 h at rt. The resulting
solution was concentrated and the residue was washed with
ether to afford 1b as a white solid (9.16 g, 100%). MS
found: (M+H)⁺ = 305.

5 **(1c)** 1,3-Dicyclohexylcarbodiimide (6.22 g, 30 mmol) was added to a solution of dipeptide **1b** (9.16 g, 26 mmol), Boc-L-valine (6.54 g, 30 mmol), 1-hydroxybenzotriazole (8.14 g, 60 mmol) and *N*-methylmorpholine (3.3 mL, 30 mmol) in dichloromethane (150 mL). After 5 h, additional *N*-
10 methylmorpholine (5 mL, 45 mmol) was added and the reaction mixture was stirred overnight at rt. The mixture was filtered, concentrated under reduced pressure, suspended in ethyl acetate, and filtered again. The filtrate was extracted with 5% sodium bicarbonate (2 x), 0.2 M
15 hydrochloric acid and brine, dried (MgSO₄) and concentrated under reduced pressure to afford **1c** as a white foam (11.1 g, 85%). MS found: (M+H)⁺ = 504.

20 **(1d)** Boc protected tripeptide **1c** (6.22 g, 12.4 mmol) was added to a solution of hydrogen chloride in 1,4-dioxane (75 mL, 4 M solution) at 0 °C. After 2 h, the reaction mixture was concentrated under reduced pressure to give hydrochloride salt **1d** as a white solid (5.39 g, 100%). MS found: (M+H)⁺ = 404.

25 **(1e)** 1,3-Dicyclohexylcarbodiimide (2.58 g, 12.5 mmol) was added to a suspension of tripeptide **1d** (5.26 g, 12.0 mmol), Cbz-L-glutamic acid-γ-*t*-butyl ester (4.07 g, 11.7 mmol), 1-hydroxybenzotriazole (3.16 g, 23.4 mmol) and *N*-
30 methylmorpholine (3 mL, 27 mmol) in dichloromethane (100 mL) and *N,N*-dimethylformamide (10 mL). The reaction mixture was stirred overnight at rt. The mixture was filtered, concentrated under reduced pressure, suspended in ethyl acetate, and filtered again. The filtrate was extracted
35 with 5% sodium bicarbonate (2 x), 0.2 M hydrochloric acid and brine, dried (MgSO₄) and concentrated under reduced pressure. The residual foam was purified by chromatography on silica gel (methanol/chloroform 1:10) to provide tetrapeptide **1e** as a white foam (8.46 g, 98%). MS found:
40 (M+H)⁺ = 723.

5

(1f) Tetrapeptide **1e** (3.00 g, 4.1 mmol) was dissolved in methanol (200 mL) and acetic acid (2 mL). Palladium hydroxide (211 mg, 20 wt.% palladium on carbon) was added and the mixture was treated with hydrogen gas (45 psi) for 4 h. The reaction mixture was concentrated under reduced pressure to afford **1f** as a pink solid (2.26 g, 100%). MS found: (M+H)⁺ = 499.

(1g) 1,3-Dicyclohexylcarbodiimide (758 mg, 3.7 mmol) was added to a solution of Boc-L-aspartic acid- β -t-butyl ester (1.00 g, 3.5 mmol) and N-hydroxysuccinimide (413 mg, 3.6 mmol) in 1,2-dimethoxyethane (5 mL). The reaction mixture was stirred overnight at rt. The resulting suspension was filtered and concentrated under reduced pressure to give **1g** as a white solid (1.48 g, 100%). MS found: (M+H)⁺ = 387.

(1h) A solution of N-hydroxysuccinimide ester **1g** (1.48 g, 3.5 mmol) was added dropwise to a suspension of tetrapeptide **1f** (2.10 g, 4.2 mmol), sodium bicarbonate (526 mg, 6.3 mmol) and triethylamine (0.880 mL, 6.3 mmol) in a mixture of water (10 mL) and 1,4-dioxane (10 mL). The reaction mixture was stirred overnight at rt. The dioxane was removed under reduced pressure and the solution was acidified to pH 1 with hydrochloric acid. The solution was extracted with ethyl acetate (2 x) and the combined organic phases washed with hydrochloric acid (0.2 M, 2 x) and brine. The solution was dried over (MgSO₄) and concentrated under reduced pressure. The residue was purified by high performance liquid chromatography (Rainin Dynamax C18 column, gradient from 50 to 80% acetonitrile in water containing 0.1% trifluoroacetic acid over 30 min, 250mg injections) to afford pentapeptide **1h** as a white solid (2.2 g, 82%). MS found: (M-H)⁻ = 769.

40

Example 2

5 H-Asp-Glu-Val-Val-Pro-(*R*)-amino(phenyl)methylboronic acid
(+)-pinanediol ester

(**2a**) (1*S*,2*S*,3*R*,5*S*)-(+) -Pinanediol (referred to hereafter as
(+)-Pinanediol) (1.70 g, 10 mmol) was added to a solution
10 of phenylboric acid (1.22 g, 10 mmol) in diethyl ether (20
mL). Magnesium sulfate was subsequently added. After 14 h,
the solution was concentrated under reduced pressure to
afford **1a** as a colorless solid (2.16 g, 84%) MS found:
(M+H)⁺ = 257.

15

(**2b**) General procedure A for the homologation of boronate
esters (Reference: Matteson, D. S.; Majumdar, D.
Organometallics **1983**, 2, 1529-1535). *n*-Butyllithium (5.2
mL, 8.3 mmol, 1.6 M solution in hexane) was added dropwise
20 to a solution of dry dichloromethane (0.640 mL, 10.0 mmol)
in tetrahydrofuran (4 mL) at -100 °C. After 30 min, a
solution of boronate ester **2a** (2.15 g, 8.4 mmol) in
tetrahydrofuran (4 mL) was added slowly dropwise, taking
care to drip the solution down the side of the flask to
25 precool it. The reaction mixture was allowed to slowly warm
to rt and then concentrated under reduced pressure. The
residue was suspended in a mixture of hexane and ethyl
acetate and filtered. The filtrate was concentrated under
reduced pressure and the residue was purified by
30 chromatography on silica gel (19:1 hexane/ethyl acetate) to
afford **2b** as a colorless solid (1.62 g, 63%). ¹H NMR
(CDCl₃, 300 MHz) δ 7.48-7.24 (m, 5H), 4.54 (s, 1H), 4.38
(dd, *J* = 9, 2 Hz), 2.38-2.29 (m, 1H), 2.26-2.18 (m, 1H),
2.11 (t, *J* = 5 Hz), 1.93-1.84 (m, 2H), 1.41 (s, 3H), 1.29
35 (s, 3H), 1.14 (d, *J* = 11 Hz), 0.83 (s, 3H).

(**2c**) General procedure B for conversion of α-chloroboronic
ester to α-aminoboronic ester. Lithium
bis(trimethylsilyl)amide (2.6 mL, 2.6 mmol, 1.0 M solution
40 in tetrahydrofuran) was added dropwise to a solution of **2b**

5 (0.791 g, 2.6 mmol) in tetrahydrofuran at -78 °C. The reaction mixture was allowed to slowly warm to rt and stir overnight. The solution was concentrated under reduced pressure. The residue was suspended in hexane, filtered through Celite and concentrated under reduced pressure. The
10 residue was dissolved in hexane (10 mL) and treated with hydrogen chloride (2.0 mL, 8.0 mmol, 4M solution in 1,4-dioxane) at -78 °C. The reaction mixture was allowed to warm to rt and then was concentrated under reduced pressure. The residue was dissolved in chloroform (2 mL)
15 and precipitated by the addition of hexane to afford **2c** (0.42 g, 50%) as a slightly yellow solid) MS found: (M+H)⁺ = 286.

(**2d**) General procedure C for coupling α -aminoboronic ester
20 to peptide: *N,N*-Diisopropylethylamine (DIEA) (0.032 mL, 0.19 mmol) was added dropwise to a solution of pentapeptide **1h** (28 mg, 0.036 mmol) and PyAOP (Carpino, L. A.; El-Faham, A.; Minor, C. A.; Albericio, F. J. *Chem. Soc., Chem. Commun.* **1994**, 201-203) (21 mg, 0.040) in *N,N*-
25 dimethylformamide. After 5 min, aminoboronic ester **2c** (19 mg, 0.059 mmol) was added. The reaction mixture was stirred at rt for 3 h and then was concentrated under reduced pressure. The residue was purified by high performance liquid chromatography (HPLC) (Rainin Dynamax C18 column,
30 gradient from 40 to 100% acetonitrile in water containing 0.1% trifluoroacetic acid over 30 min) to afford **2d** (22.6 mg, 61%) as a white foam. MS found: (M-H)⁻ = 1036.

(**2e**) Peptide boronic ester **2d** (12.4 mg, 0.012 mmol) was
35 dissolved in a mixture of trifluoroacetic acid (TFA) (1 mL), triisopropylsilane (0.050 mL) and dichloromethane (0.050 mL). The reaction mixture was stirred at rt for 4 h and then was concentrated under reduced pressure. The residue was purified by high performance liquid
40 chromatography (Rainin Dynamax C18 column, gradient from 20 to 70% acetonitrile in water containing 0.1%

5 trifluoroacetic acid over 30 min) to afford **2** . MS found:
(M+H)⁺ = 825.5.

Example 3

10 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic
acid (+)-pinanediol ester

(**3a**) A solution of triisopropyl borate(5.75 mL, 25 mmol) in diethyl ether (15 mL) was added slowly dropwise to diethyl ether (10 mL) at -78 °C. Phenethyl magnesium chloride (25
15 mL, 25 mmol, 1M in tetrahydrofuran) was added slowly dropwise at the same time. The reaction mixture was allowed to warm slowly to rt and stirred overnight. The resulting suspension was cooled in an ice bath and neutralized by addition of sulfuric acid (2.65 mL) in water (4.5 mL).
20 After stirring 2 h, the reaction mixture was diluted with water (15 mL) and extracted with diethyl ether (2 x). The organic layers were dried (Na₂SO₄) and (+)-pinanediol (4.25 g, 25 mmol) was added. The solution was stirred for several days and was then filtered and concentrated under reduced
25 pressure. The residue was by chromatography on silica gel (hexane/ethyl acetate 9:1) to provide phenethyl boronate **3a** as a colorless oil (3.6 g, 51%).

(**3b**) Following a procedure analogous to (2b),
30 Phenethylboronate **3a** (3.6 g, 12.7 mmol) was treated with *n*-butyllithium and dichloromethane in tetrahydrofuran to provide the desired α-chloroboronic ester **3b** as an orange oil which was a 2:1 mixture of starting material and product(3.5 g, 55%) after chromatography on silica gel.

35
(**3c**) Following a procedure analogous to (2c), α-chloroboronic ester **3b** (3.5 g, 2:1 mixture of **3b** and **3a**, 6.9 mmol) was converted to the aminoboronic ester hydrochloride **3c** by treatment with lithium
40 bis(trimethylsilyl)amide followed by hydrogen chloride. The

5 desired product **3c** was obtained as a white solid (1.44 g, 59%). MS found: $(M+H)^+ = 314$.

(**3d**) Following a procedure analogous to (2d), α -aminoboronic ester **3c** (20 mg, 0.057 mmol) was coupled to
10 pentapeptide **1h** (25 mg, 0.032 mmol) with PyAOP and DIEA. The desired hexapeptide **3d** (8 mg, 23%) was obtained after purification by HPLC. MS found: $(M-H)^- = 1064$.

(**3e**) Following a procedure analogous to (2e), the
15 hexapeptide **3d** (5 mg, 0.005 mmol) was deprotected with TFA and triisopropylsilane to afford the desired hexapeptide **3e** (4 mg, 100 %) as a white solid after purification by HPLC. HRMS found: $(M+H)^+ = 853.4856$.

20 **Example 4**

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-4-phenylbutylboronic
acid (+)-pinanediol ester

(**4a**) Magnesium (540 mg, 22.2 mmol) was suspended in
25 tetrahydrofuran (20 mL) and treated with ethylene bromide (5 drops) to initiate Grignard reaction. After a cloudy, grey precipitate formed, 1-bromo-3-phenylpropane (3.0 mL, 20 mmol) in tetrahydrofuran (20 mL) was added slowly dropwise. The solution was refluxed 30 min to give a clear,
30 brown solution of grignard reagent **4a**. This material was used without further characterization.

(**4b**) Using a procedure analogous to (3a), Grignard reagent
4a (20 mmol) was reacted with triisopropyl borate and (+)-
35 pinanediol. Silica gel chromatography (9:1 hexane/ethyl acetate) afforded the desired boronic ester **4b** as a pale yellow oil (1.28 g, 21%).

(**4c**) Using a procedure analogous to (2b), boronic ester **4b**
40 (1.28 g, 4.29 mmol) was treated with *n*-butyllithium and dichloromethane in tetrahydrofuran to provide the desired

5 α -chloroboronic ester **4c** as a clear oil (0.31 g, 21%) after chromatography on silica gel.

(**4d**) Following a procedure analogous to (2c), α -chloroboronic ester **4c** (0.31 g, 0.90 mmol) was converted to
10 the aminoboronic ester hydrochloride **4d** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **4d** was obtained as a white solid. MS found: (M+H)⁺ = 328.2.

15 (**4e**) Following a procedure analogous to (2d), α -aminoboronic ester (**4d**) (28 mg, 0.077 mmol) was coupled to pentapeptide **1h** (30 mg, 0.038 mmol) with PyAOP and DIEA and purified by HPLC to afford the desired hexapeptide **4e**.

20 (**4f**) Following a procedure analogous to (2e), the hexapeptide **4e** (5 mg, 0.005 mmol) was deprotected with TFA and triisopropylsilane and purified by HPLC to afford the desired hexapeptide **4f** (1 mg) as a white solid. HRMS found: (M+H)⁺ = 867.5055.

25

Example 5

H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-5-phenylpentylboronic acid (+)-pinanediol ester

30 (**5a**) Using a procedure analogous to (4a), 1-chloro-4-phenylbutane was reacted with magnesium to prepare Grignard reagent **5a**. This material was used without further characterization.

35 (**5b**) Using a procedure analogous to (3a), Grignard reagent **5a** (20 mmol) was reacted with triisopropyl borate and (+)-pinanediol. Silica gel chromatography (19:1 hexane/ethyl acetate) afforded the desired boronic ester **5b** as a colorless oil (3.15 g, 50%).

40

5 (5c) Using a procedure analogous to (2b), boronic ester 5b (3.15 g, 10 mmol) was treated with *n*-butyllithium and dichloromethane in tetrahydrofuran to provide a 2:1 mixture of the desired α -chloroboronic ester 5c and starting material 5b as a clear oil (3.2 g, 59%).

10

(5d) Following a procedure analogous to (2c), α -chloroboronic ester 5c (3.2 g, 5.90 mmol) was converted to the aminoboronic ester hydrochloride 5d by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product (5d) was obtained as a white solid. MS found: $(M+H)^+ = 342.3$.

(5e) Following a procedure analogous to (2d), α -aminoboronic ester (5d) (40 mg, 0.11 mmol) was coupled to pentapeptide 1h (32 mg, 0.040 mmol) with PyAOP and DIEA and purified by HPLC to afford the desired hexapeptide 5e. HRMS found: $(M+H)^+ = 1093.695$.

(5f) Following a procedure analogous to (2e), the hexapeptide 5e was deprotected with TFA and triisopropylsilane and purified by HPLC to afford the desired hexapeptide 5f. HRMS found: $(M+H)^+ = 881.5224$.

Example 7

30 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2-naphthyl)propylboronic acid (+)-pinanediol ester

(7a) Using a procedure analogous to (4a), 1-(2-bromoethyl)naphthalene (4.70 g, 20 mmol) was reacted with magnesium to prepare Grignard reagent 7a. This material was used without further characterization.

(7b) Using a procedure analogous to (3a), Grignard reagent 7a (20 mmol) was reacted with triisopropyl borate and (+)-pinanediol. Silica gel chromatography (99:1 hexane/ethyl

40

5 acetate) afforded the desired boronic ester **7b** as a colorless oil (1.34 g, 20%).

(**7c**) Using a procedure analogous to (2b), boronic ester **7b** (1.34 g, 4.01 mmol) was treated with *n*-butyllithium and
10 dichloromethane in tetrahydrofuran to provide a 4:1 mixture of the desired α -chloroboronic ester **7c** and starting material **7b** as a clear oil (0.18 g, 12%).

(**7d**) Following a procedure analogous to (2c), α -
15 chloroboronic ester **7c** (0.18 g, 0.47 mmol) was converted to the aminoboronic ester hydrochloride **7d** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **7d** was obtained as a pink solid (0.120 g, 64%). MS found: (M+H)⁺ = 364.

20

(**7e**) Following a procedure analogous to (2d), α -aminoboronic ester (**7d**) (40 mg, 0.11 mmol) was coupled to pentapeptide **1h** (29 mg, 0.038 mmol) with PyAOP and DIEA and purified by HPLC to afford the desired hexapeptide **7e**. MS
25 found: (M+H)⁺ = 1116

(**7f**) Following a procedure analogous to (2e), the hexapeptide **7e** was deprotected with TFA and triisopropylsilane and purified by HPLC to afford the
30 desired hexapeptide **7f**. HRMS found: (M+H)⁺ = 903.5050.

Example 8

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2-methyl)phenylpropylboronic acid (+)-pinanediol ester

35

(**8a**) Catecholborane (3.59 mL, 34 mmol) was added dropwise to 2-methylstyrene (3.87 mL, 30 mmol). The reaction mixture was heated to 70 °C and allowed to stir overnight. A solution of (+)-pinanediol (5 g, 29 mmol) in diethyl ether
40 (100 mL) was added dropwise to the catecholborane reaction

5 mixture. The solution was allowed to stir at rt for several days, and then was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (10:1 hexane/ethyl acetate) to provide the desired boronic ester **8a** as a colorless oil (6.75 g, 75%).

10

(**8b**) *n*-Butyllithium (6.9 mL, 11 mmol, 1.6 M in hexane) was added slowly dropwise to a solution of dichloromethane (0.96 mL, 15 mmol) in tetrahydrofuran (20 mL) at -100 °C. After 30 min, a solution of boronic ester **8a** (2.98 g, 10 mmol) in tetrahydrofuran (5 mL) was added slowly dropwise. After 1 hr, a solution of ZnCl₂ (0.69 g, 5 mmol, dried at 150 °C for several hr under vacuum) in tetrahydrofuran (5 mL) was added and the reaction mixture was allowed to slowly warm to rt and stir overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in diethyl ether and washed with water (2 x). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by HPLC (Rainin Dynamax 60Å silica column) in 10:7 hexane/dichloromethane to afford the desired α -chloroboronic ester **8b** as a colorless oil (0.48 g, 14%).

(**8c**) Following a procedure analogous to (2c), α -chloroboronic ester **8b** (0.48 g, 1.4 mmol) was converted to the aminoboronic ester hydrochloride **8c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product (**8c**) was obtained as a white solid (0.243 g, 48%). MS found: (M+H)⁺ = 328.

35 (**8d**) Following a procedure analogous to (2d), α -aminoboronic ester **8c** (30 mg, 0.082 mmol) was coupled to pentapeptide **1h** (34 mg, 0.044 mmol) with PyAOP and DIEA. The crude protected pentapeptide was deprotected following a procedure analogous to (2e) and purified by HPLC to afford the desired hexapeptide **8d**. HRMS found: (M+H)⁺ = 867.5012.

40

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Example 9

H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(3-methyl)phenylpropylboronic acid (+)-pinanediol ester

- 10 **(9a)** Following a procedure analogous to (8a), 3-methylstyrene (3.54 g, 30 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **9a** as a yellow oil (2.93 g, 33%).
- 15 **(9b)** Following a procedure analogous to (8b), boronic ester **9a** (2.93 g, 9.8 mmol) was treated with *n*-butyllithium, dichloromethane, and ZnCl₂. After HPLC purification (10:9 hexane/dichloromethane), the desired α -chloroboronic ester **9b** was obtained as a colorless oil (0.38 g, 11%).
- 20 **(9c)** Following a procedure analogous to (2c), α -chloroboronic ester **9b** (0.38 g, 4.5 mmol) was converted to the aminoboronic ester hydrochloride **9c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen
- 25 chloride. The desired product **9c** was obtained as a white solid. MS found: (M+H)⁺ = 328.
- (9d)** Following a procedure analogous to (8d), α -aminoboronic ester **9c** (34 mg, 0.093 mmol) was coupled to
- 30 pentapeptide **1h** (33 mg, 0.043 mmol) with PyAOP and DIEA. The crude hexapeptide was deprotected with TFA and purified by HPLC to afford the desired hexapeptide **9d**. HRMS found: (M+H)⁺ = 867.5041.

35

Example 10

H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(4-methyl)phenylpropylboronic acid (+)-pinanediol ester

- (10a)** Following a procedure analogous to (8a), 4-methylstyrene (3.95 g, 30 mmol) was treated with
- 40

100

5 catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **10a** as a white solid (1.55 g, 17%).

(**10b**) Following a procedure analogous to (8b), boronic ester **10a** (0.420 g, 1.4 mmol) was treated with *n*-
10 butyllithium, dichloromethane, and ZnCl₂. After HPLC purification (10:8 hexane/dichloromethane), the desired α -chloroboronic ester **10b** was obtained as a colorless oil (0.23 g, 47%).

15 (**10c**) Following a procedure analogous to (2c), α -chloroboronic ester **10b** (0.23 g, 0.66 mmol) was converted to the aminoboronic ester hydrochloride **10c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen
chloride. The desired product **10c** was obtained as a sticky
20 solid (143 mg, 59%). MS found: (M+H)⁺ = 328.

(**10d**) Following a procedure analogous to (8d), α -aminoboronic ester **10c** (37 mg, 0.10 mmol) was coupled to pentapeptide **1h** (36 mg, 0.046 mmol) with PyAOP and DIEA.
25 The crude hexapeptide was deprotected with TFA and purified by HPLC to afford the desired hexapeptide **10d**. HRMS found: (M+H)⁺ = 867.5055.

Example 11

30 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-3-(1,1'-biphenyl)-4-ylpropylboronic acid (+)-pinanediol ester

(**11a**) Following a procedure analogous to (8a), 4-vinyl biphenyl (5.4 g, 30 mmol) was treated with catecholborane,
35 followed by (+)-pinanediol to provide the desired boronic ester **11a** as a pale yellow solid (7.53 g, 71%).

(**11b**) Following a procedure analogous to (8b), boronic ester **11a** (2.28 g, 6.3 mmol) was treated with *n*-
40 butyllithium, dichloromethane, and ZnCl₂. After HPLC

5 purification (11:4 hexane/dichloromethane), the desired α -chloroboronic ester **11b** was obtained as a colorless oil (0.85 g, 33%).

10 (**11c**) Following a procedure analogous to (2c), α -chloroboronic ester **11b** (0.85 g, 2.1 mmol) was converted to the aminoboronic ester hydrochloride **11c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **11c** was obtained as a brown solid (0.54 g, 60%). MS found: $(M+H)^+ = 390$.

15

(**11d**) Following a procedure analogous to (8d), α -aminoboronic ester **11c** (40 mg, 0.094 mmol) was coupled to pentapeptide **1h** (33 mg, 0.043 mmol) with PyAOP and DIEA. The crude hexapeptide was deprotected with TFA and purified
20 by HPLC to afford the desired hexapeptide **11d**. HRMS found: $(M+H)^+ = 929.5210$.

Example 12

25 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2,5-dimethyl)phenylpropylboronic acid (+)-pinanediol ester

(**12a**) Following a procedure analogous to (8a), 2,5-dimethylstyrene (3.97 g, 30 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the
30 desired boronic ester **12a** as a colorless oil (7.04 g, 75%).

(**12b**) Following a procedure analogous to (8b), boronic ester **12a** (7.04 g, 22.5 mmol) was treated with *n*-butyllithium, dichloromethane, and $ZnCl_2$. After HPLC
35 purification (11:6 hexane/dichloromethane), the desired α -chloroboronic ester **12b** was obtained as a colorless oil (1.94 g, 24%).

(**12c**) Following a procedure analogous to (2c), α -chloroboronic ester **12b** (1.94 g, 5.4 mmol) was converted to
40

5 the aminoboronic ester hydrochloride **12c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **12c** was obtained as a white solid. MS found: $(M+H)^+ = 342$.

10 (**12d**) Following a procedure analogous to (8d), α -aminoboronic ester **12c** (27 mg, 0.079 mmol) was coupled to pentapeptide **1h** (33 mg, 0.043 mmol) with PyAOP and DIEA. The crude hexapeptide was deprotected with TFA and purified by HPLC to afford the desired hexapeptide **11d** (3 mg, 8%).
15 HRMS found: $(M+H)^+ = 881.5185$.

Example 13

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2,4-dimethyl)phenylpropylboronic acid (+)-pinanediol ester

20

(**13a**) Following a procedure analogous to (8a), 2,4-dimethylstyrene (3.97 g, 30 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **13a** as a colorless oil (7.77 g, 82%).

25

(**13b**) *n*-Butyllithium (7.6 mL, 12.2 mmol, 1.6 M in hexane) was added dropwise over 50 min to a solution of dichloromethane (1.1 mL, 17 mmol) in tetrahydrofuran (40 mL) at -100 °C. After 20 min, a solution of boronic ester
30 **13a** (3.47 g, 11 mmol) in tetrahydrofuran (5 mL) was added dropwise over 20 min. The reaction mixture was allowed to slowly warm to rt and stir overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in diethyl ether and washed with 0.1 N sulfuric
35 acid (2 x). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by HPLC (Rainin Dynamax 60Å silica column) in 11:5 hexane/dichloromethane to afford the desired α -chloroboronic ester **13b** as a colorless oil (1.76 g, 44%).

40

5 **(13c)** Following a procedure analogous to (2c), α -chloroboronic ester **13b** (1.76 g, 4.9 mmol) was converted to the aminoboronic ester hydrochloride **13c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **13c** was obtained as a tan
10 solid. MS found: $(M+H)^+ = 342.3$.

(13d) Following a procedure analogous to (8d), α -aminoboronic ester **13c** (34 mg, 0.099 mmol) was coupled to pentapeptide **1h** (30 mg, 0.039 mmol) with PyAOP and DIEA.
15 The crude hexapeptide was deprotected with TFA and purified by HPLC to afford the desired hexapeptide **13d** (6 mg, 17%). HRMS found: $(M+H)^+ = 881.5192$.

Example 14

20 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-trifluoromethyl)phenylpropylboronic acid (+)-pinanediol ester

(14a) Following a procedure analogous to (8a), 4-trifluoromethylstyrene (3.0 g, 17 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **14a** as a colorless oil (3.1 g, 51%).
25

(14b) Following a procedure analogous to (13b), boronic ester **14a** (3.12 g, 22.5 mmol) was treated with *n*-butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **14b** was obtained as a colorless oil (1.39 g, 39%).
30

(14c) Following a procedure analogous to (2c), α -chloroboronic ester **14b** (1.39 g, 3.5 mmol) was converted to the aminoboronic ester hydrochloride **14c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **14c** was obtained as a yellow
40 solid (0.65 g, 44%). MS found: $(M+H)^+ = 382$.

5

(**14d**) Following a procedure analogous to (8d), α -aminoboronic ester **14c** (28 mg, 0.054 mmol) was coupled to pentapeptide **1h** (32 mg, 0.042 mmol) with PyAOP and DIEA. The crude hexapeptide was deprotected with TFA and purified
10 by HPLC to afford the desired hexapeptide **14d** (6 mg, 16%). HRMS found: $(M+H)^+ = 921.4785$.

Example 15

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(3-
15 trifluoromethyl)phenylpropylboronic acid (+)-pinanediol
ester

(**15a**) Following a procedure analogous to (8a), 3-trifluoromethylstyrene (2.0 g, 11.6 mmol) was treated with
20 catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **15a** as a colorless oil (2.24 g, 55%) after chromatography on silica gel (9:1 hexane ethyl acetate).

25 (**15b**) Following a procedure analogous to (13b), boronic ester **15a** (2.24 g, 6.4 mmol) was treated with *n*-butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **15b** was obtained as a colorless oil (0.70 g, 27%).

30

(**15c**) Following a procedure analogous to (2c), α -chloroboronic ester **15b** (0.70 g, 1.75 mmol) was converted to the aminoboronic ester hydrochloride **15c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen
35 chloride. The desired product **15c** was obtained as a tan solid (0.41 g, 56%). MS found: $(M+H)^+ = 382$.

(**15d**) Following a procedure analogous to (8d), α -aminoboronic ester **15c** (39 mg, 0.093 mmol) was coupled to
40 pentapeptide **1h** (40 mg, 0.052 mmol) with PyAOP and DIEA.

5 The crude hexapeptide was deprotected with TFA and purified by HPLC to afford the desired hexapeptide **15d**. HRMS found: $(M+H)^+ = 921.4765$.

Example 16

10 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-fluoro)phenylpropylboronic acid (+)-pinanediol ester

(**16a**) Following a procedure analogous to (8a), 4-fluorostyrene (2.44 g, 20.0 mmol) was treated with
15 catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **16a** as a colorless oil (3.86 g, 64%).

(**16b**) Following a procedure analogous to (13b), boronic ester **16a** (3.86 g, 12.8 mmol) was treated with *n*-
20 butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **16b** was obtained as a colorless oil (1.57 g, 35%).

(**16c**) Following a procedure analogous to (2c), α -
25 chloroboronic ester **16b** (1.57 g, 4.48 mmol) was converted to the aminoboronic ester hydrochloride **16c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **16c** was obtained as a tan solid (0.63 g, 38%). MS found: $(M+H)^+ = 332$.

30 (**16d**) Following a procedure analogous to (8d), α -aminoboronic ester **16c** (36 mg, 0.097 mmol) was coupled to pentapeptide **1h** (38 mg, 0.049 mmol) with PyAOP and DIEA. The crude hexapeptide was deprotected with TFA and purified
35 by HPLC to afford the desired hexapeptide **15d**. HRMS found: $(M+H)^+ = 871.4816$.

Example 17

40 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-phenoxy)phenylpropylboronic acid (+)-pinanediol ester

5

(17a) Following a procedure analogous to (8a), 4-phenoxystyrene (3.92 g, 20.0 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **17a** as a colorless oil (2.42 g, 32%).

10

(17b) Following a procedure analogous to (13b), boronic ester **17a** (2.42 g, 6.43 mmol) was treated with *n*-butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **17b** was obtained as a colorless oil (0.81 g, 30%).

15

(17c) Following a procedure analogous to (2c), α -chloroboronic ester **17b** (0.74 g, 1.73 mmol) was converted to the aminoboronic ester hydrochloride **17c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **17c** was obtained as a white solid. MS found: (M+H)⁺ = 406.

20

(17d) 1-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (EDCI) (10 mg, 0.052 mmol) and sodium bicarbonate (20 mg, 0.24 mmol) were added in one portion to a solution of α -aminoboronic ester **17c** (26 mg, 0.059 mmol), pentapeptide **1h** (30 mg, 0.039 mmol), and 1-hydroxy-7-azabenzotriazole (HOAt) (8 mg, 0.059) in dichloromethane (1 mL) and *N,N*-dimethylformamide (0.2 mL) at 0 °C. The reaction mixture was stirred for 1 hr, warmed to rt, and allowed to stir an additional 1 hr. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (9:1 chloroform/methanol) to afford protected hexapeptide **17d** as a white solid (26 mg, 58%). MS found: (M+Na)⁺ = 1180.

30

35

(17e) Peptide boronic ester **17d** (21 mg, 0.018 mmol) was dissolved in a mixture of trifluoroacetic acid (TFA) (1 mL), triisopropylsilane (0.050 mL) and dichloromethane

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5 (0.050 mL). The reaction mixture was stirred at rt for 2 h
and then was concentrated under reduced pressure. The
residue was purified by high performance liquid
chromatography (Rainin Dynamax C18 column, gradient from 20
to 70% acetonitrile in water containing 0.1%
10 trifluoroacetic acid over 30 min) to afford hexapeptide
17e. HRMS found: (M+H)⁺ = 945.5138.

Example 18

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-
15 isopropyl)phenylpropylboronic acid (+)-pinanediol ester

(**18a**) Following a procedure analogous to (8a), 4-
isopropylstyrene (2.00 g, 13.7 mmol) was treated with
catecholborane, followed by (+)-pinanediol to provide the
20 desired boronic ester **18a** as a colorless solid (2.71 g,
61%).

(**18b**) Following a procedure analogous to (13b), boronic
ester **18a** (2.71 g, 8.31 mmol) was treated with *n*-
25 butyllithium and dichloromethane. After HPLC purification,
the desired α -chloroboronic ester **18b** was obtained as a
colorless oil (1.07 g, 34%).

(**18c**) Following a procedure analogous to (2c), α -
30 chloroboronic ester **18b** (1.07 g, 2.86 mmol) was converted
to the aminoboronic ester hydrochloride **18c** by treatment
with lithium bis(trimethylsilyl)amide followed by hydrogen
chloride. The desired product **18c** was obtained as a white
solid. MS found: (M+H)⁺ = 356.

35

(**18d**) Following a procedure analogous to (17d), α -
aminoboronic ester **18c** (26 mg, 0.066 mmol) was coupled to
pentapeptide **1h** (30 mg, 0.039 mmol) with EDCI, HOAt, and
sodium bicarbonate. The crude hexapeptide was deprotected
40 with TFA, following a procedure analogous to (17e), and

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5 purified by HPLC to afford the desired hexapeptide **18d**.
HRMS found: $(M+H)^+ = 895.5381$.

Exempl 19

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-
10 cyclohexyl)phenylpropylboronic acid (+)-pinanediol ester

(**19a**) Following a procedure analogous to (8a), 4-
cyclohexylstyrene (2.45 g, 13.2 mmol) was treated with
catecholborane, followed by (+)-pinanediol to provide the
15 desired boronic ester **19a** as a colorless solid (2.78 g,
58%).

(**19b**) Following a procedure analogous to (13b), boronic
ester **19a** (3.4 g, 9.3 mmol) was treated with *n*-butyllithium
20 and dichloromethane. After HPLC purification, the desired
 α -chloroboronic ester **19b** was obtained as a colorless oil
(1.08 g, 28%).

(**19c**) Following a procedure analogous to (2c), α -
25 chloroboronic ester **19b** (1.0 g, 2.4 mmol) was converted to
the aminoboronic ester hydrochloride **19c** by treatment with
lithium bis(trimethylsilyl)amide followed by hydrogen
chloride. The desired product **19c** was obtained as a white
solid (290 mg, 26%). MS found: $(M+H)^+ = 396$.

30
(**19d**) Following a procedure analogous to (17d), α -
aminoboronic ester **19c** (25 mg, 0.058 mmol) was coupled to
pentapeptide **1h** (32 mg, 0.042 mmol) with EDCI, HOAt, and
sodium bicarbonate. The crude hexapeptide was deprotected
35 with TFA, following a procedure analogous to (17e), and
purified by HPLC to afford the desired hexapeptide **19d**.
HRMS found: $(M+H)^+ = 935.5638$.

Example 20

5 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-*tert*-
butyl)phenylpropylboronic acid (+)-pinanediol ester

(20a) Following a procedure analogous to (8a), 4-*t*-
butylstyrene (3.21 g, 20 mmol) was treated with
10 catecholborane, followed by (+)-pinanediol to provide the
desired boronic ester **20a** as a dark orange solid (3.57 g,
52%).

(20b) Following a procedure analogous to (13b), boronic
15 ester **20a** (3.57 g, 10.5 mmol) was treated with *n*-
butyllithium and dichloromethane. After HPLC purification,
the desired α -chloroboronic ester **20b** was obtained as a
colorless oil (0.68 g, 17%).

20 (20c) Following a procedure analogous to (2c), α -
chloroboronic ester **20b** (0.68 g, 1.8 mmol) was converted to
the aminoboronic ester hydrochloride **20c** by treatment with
lithium bis(trimethylsilyl)amide followed by hydrogen
chloride. The desired product **20c** was obtained as a white
25 solid (70 mg, 10%). MS found: (M+H)⁺ = 370.

(20d) Following a procedure analogous to (17d), α -
aminoboronic ester **20c** (24 mg, 0.059 mmol) was coupled to
pentapeptide **1h** (30 mg, 0.039 mmol) with EDCI, HOAt, and
30 sodium bicarbonate. The crude hexapeptide was deprotected
with TFA, following a procedure analogous to (17e), and
purified by HPLC to afford the desired hexapeptide **20d**.
HRMS found: (M+H)⁺ = 909.5504.

35 **Example 21**

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-
methoxy)phenylpropylboronic acid (+)-pinanediol ester

(21a) Following a procedure analogous to (8a), 4-
40 methoxystyrene (2.68 g, 20 mmol) was treated with

5 catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **21a** as a colorless oil (4.3 g, 68%).

(**21b**) Following a procedure analogous to (13b), boronic ester **21a** (4.3 g, 13.7 mmol) was treated with *n*-
10 butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **21b** was obtained as a colorless oil (1.98 g, 40%).

(**21c**) Following a procedure analogous to (2c), α -
15 chloroboronic ester **21b** (1.98 g, 5.5 mmol) was converted to the aminoboronic ester hydrochloride **21c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **21c** was obtained as a white solid (400 mg, 19%). MS found: (M+H)⁺ = 344.

20

(**21d**) Following a procedure analogous to (17d), α -aminoboronic ester **21c** (22 mg, 0.058 mmol) was coupled to pentapeptide **1h** (31 mg, 0.040 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude hexapeptide was deprotected
25 with TFA, following a procedure analogous to (17e), and purified by HPLC to afford the desired hexapeptide **21d**. HRMS found: (M+H)⁺ = 883.4999.

Example 22

30 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-chloro)phenylpropylboronic acid (+)-pinanediol ester

(**22a**) Following a procedure analogous to (8a), 4-chlorostyrene (2.77 g, 20 mmol) was treated with
35 catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **22a** as a colorless solid (3.22 g, 50%).

(**22b**) Following a procedure analogous to (13b), boronic ester **22a** (3.22 g, 10.1 mmol) was treated with *n*-
40

5 butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **22b** was obtained as a colorless oil (1.32 g, 36%).

(**22c**) Following a procedure analogous to (2c), α -chloroboronic ester **22b** (1.32 g, 3.6 mmol) was converted to the aminoboronic ester hydrochloride **22c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **22c** was obtained as a white solid (700 mg, 51%). MS found: (M+H)⁺ = 348.

15

(**22d**) Following a procedure analogous to (17d), α -aminoboronic ester **22c** (23 mg, 0.060 mmol) was coupled to pentapeptide **1h** (30 mg, 0.039 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude hexapeptide was deprotected with TFA, following a procedure analogous to (17e), and purified by HPLC to afford the desired hexapeptide **22d**. HRMS found: (M+H)⁺ = 887.4518.

Example 23

25 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-bromo)phenylpropylboronic acid (+)-pinanediol ester

(**23a**) Following a procedure analogous to (8a), 4-bromostyrene (3.66 g, 20 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **23a** as a white solid (3.01 g, 42%).

(**23b**) Following a procedure analogous to (13b), boronic ester **23a** (2.67 g, 7.35 mmol) was treated with *n*-butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **23b** was obtained as a colorless oil (0.64 g, 21%).

(**23c**) Following a procedure analogous to (2c), α -chloroboronic ester **23b** (0.64 g, 1.56 mmol) was converted

40

5 to the aminoboronic ester hydrochloride **23c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **23c** was obtained as a white solid (0.71 mg, 100%). MS found: $(M+H)^+ = 392$.

10 **(23d)** Following a procedure analogous to (17d), α -aminoboronic ester **23c** (25 mg, 0.058 mmol) was coupled to pentapeptide **1h** (33 mg, 0.043 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude hexapeptide was deprotected with TFA, following a procedure analogous to (17e), and
15 purified by HPLC to afford the desired hexapeptide **23d**. HRMS found: $(M+H)^+ = 931.3968$.

Example 24

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2-
20 fluoro)phenylpropylboronic acid (+)-pinanediol ester

(24a) Following a procedure analogous to (8a), 2-fluorostyrene (2.4 g, 20 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the
25 desired boronic ester **24a** as a colorless oil (1.78 g, 30%).

(24b) Following a procedure analogous to (13b), boronic ester **24a** (1.78 g, 5.89 mmol) was treated with *n*-butyllithium and dichloromethane. After HPLC purification,
30 the desired α -chloroboronic ester **24b** was obtained as a colorless oil (1.0 g, 48%).

(24c) Following a procedure analogous to (2c), α -chloroboronic ester **24b** (1.00 g, 2.85 mmol) was converted
35 to the aminoboronic ester hydrochloride **24c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **24c** was obtained as a white solid (0.37 mg, 35%). MS found: $(M+H)^+ = 332$.

5 **(24d)** Following a procedure analogous to (17d), α -aminoboronic ester **24c** (21 mg, 0.057 mmol) was coupled to pentapeptide **1h** (32 mg, 0.042 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude hexapeptide was deprotected with TFA, following a procedure analogous to (17e), and
10 purified by HPLC to afford the desired hexapeptide **24d**.
HRMS found: $(M+H)^+ = 871.4793$.

Example 25

 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(3-
15 fluoro)phenylpropylboronic acid (+)-pinanediol ester

(25a) Following a procedure analogous to (8a), 3-fluorostyrene (2.44 g, 20 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the
20 desired boronic ester **25a** as a colorless oil (3.4 g, 56%).

(25b) Following a procedure analogous to (13b), boronic ester **25a** (1.7 g, 5.6 mmol) was treated with *n*-butyllithium and dichloromethane. After HPLC purification, the desired
25 α -chloroboronic ester **25b** was obtained as a colorless oil (0.865 g, 44%).

(25c) Following a procedure analogous to (2c), α -chloroboronic ester **25b** (0.87 g, 2.48 mmol) was converted
30 to the aminoboronic ester hydrochloride **25c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **25c** was obtained as a white solid (0.300 mg, 33%). MS found: $(M+H)^+ = 332$.

35 **(25d)** Following a procedure analogous to (17d), α -aminoboronic ester **25c** (21 mg, 0.057 mmol) was coupled to pentapeptide **1h** (32 mg, 0.042 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude hexapeptide was deprotected with TFA, following a procedure analogous to (17e), and

5 purified by HPLC to afford the desired hexapeptide **25d**.

HRMS found: $(M-H)^- = 869.4623$.

Example 26

10 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(2,6-
difluoro)phenylpropylboronic acid (+)-pinanediol ester

(**26a**) Following a procedure analogous to (8a), 2,6-difluorostyrene (3.0 g, 21.4 mmol) was treated with catecholborane, followed by (+)-pinanediol to provide the
15 desired boronic ester **26a** as a colorless oil (0.933 g, 14%).

(**26b**) Following a procedure analogous to (13b), boronic ester **26a** (0.93 g, 2.9 mmol) was treated with *n*-
20 butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **26b** was obtained as a colorless oil (0.22 g, 20%).

(**26c**) Following a procedure analogous to (2c), α -
25 chloroboronic ester **26b** (0.22 g, 0.60 mmol) was converted to the aminoboronic ester hydrochloride **26c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **26c** was obtained as a white solid (0.150 mg, 65%). MS found: $(M+H)^+ = 350$.

30 (**26d**) Following a procedure analogous to (17d), α -aminoboronic ester **26c** (30 mg, 0.081 mmol) was coupled to pentapeptide **1h** (36 mg, 0.047 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude hexapeptide was deprotected
35 with TFA, following a procedure analogous to (17e), and purified by HPLC to afford the desired hexapeptide **26d**.
HRMS found: $(M+H)^+ = 889.4685$.

Example 27

5 H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-(4-hydroxy)phenylpropylboronic acid (+)-pinanediol ester

(27a) Following a procedure analogous to (8a), 4-*t*-butoxystyrene (3.53 g, 20 mmol) was treated with
10 catecholborane, followed by (+)-pinanediol to provide the desired boronic ester **27a** as a colorless oil (2.1 g, 29%).

(27b) Following a procedure analogous to (13b), boronic ester **27a** (1.99 g, 5.6 mmol) was treated with *n*-
15 butyllithium and dichloromethane. After HPLC purification, the desired α -chloroboronic ester **27b** was obtained as a colorless oil (0.82 g, 36%).

(27c) Following a procedure analogous to (2c), α -
20 chloroboronic ester **27b** (0.82 g, 2.02 mmol) was converted to the aminoboronic ester hydrochloride **27c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **27c** was obtained as a white solid (0.180 mg, 24%). MS found: (M+H)⁺ = 330.

25 (27d) Following a procedure analogous to (17d), α -aminoboronic ester **27c** (24 mg, 0.066 mmol) was coupled to pentapeptide **1h** (30 mg, 0.039 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude hexapeptide was deprotected
30 with TFA, following a procedure analogous to (17e), and purified by HPLC to afford the desired hexapeptide **27d**. HRMS found: (M+H)⁺ = 869.4838.

Example 28

35 Ac-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester

(28a) Isobutyl chloroformate (2.9 mL, 22 mmol) was added dropwise to a suspension of *N*-acetyl-L-valine (3.18 g, 20
40 mmol) and *N*-methymorpholine (2.4 mL, 22 mmol) in

5 dichloromethane (50 mL) at -10 °C. The reaction mixture was stirred 30 min. A solution of L-proline benzyl ester (4.83 g, 20 mmol) and *N*-methylemorpholine (2.4 mL, 22 mmol) in dichloromethane (20 mL) was added portionwise. The reaction was stirred for 1 h at -10 °C and then warmed to rt and
10 stirred overnight. The reaction mixture was washed with 1 N hydrochloric acid (2 x) and brine (1 x), dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (9:1 chloroform/methanol) to afford 7.3 g (100%) of a colorless
15 oil. MS found: (M+H)⁺ = 347.2.

(**28b**) A suspension of dipeptide **28a** and palladium hydroxide (220 mg, 20 wt. % on charcoal) in methanol (50 mL) and acetic acid (0.5 mL) was hydrogenated (45 psi) for 1.5 h.
20 The reaction mixture was filtered and concentrated under reduced pressure to provide dipeptide **28b** (2.44 g, 92%). MS found: (M+H)⁺ = 257.3.

(**28c**) Following a procedure analogous to (17d), α-aminoboronic ester **3c** (35 mg, 0.10 mmol) was coupled to dipeptide **28b** (26 mg, 0.10 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude tripeptide was purified by HPLC to afford the desired tripeptide boronic ester **28c**.
HRMS found: (M+H)⁺ = 552.3598.

30

Example 29

Ac-Val-Pro-(1*R*)-1-amino-3-(4-trifluoromethyl)phenylpropylboronic acid (+)-pinanediol ester

35 (**29a**) Following a procedure analogous to (17d), α-aminoboronic ester **14c** (42 mg, 0.10 mmol) was coupled to dipeptide **28b** (26 mg, 0.10 mmol) with EDCI, HOAt, and sodium bicarbonate. The crude tripeptide was purified by HPLC to afford the desired tripeptide boronic ester **29a**.
40 HRMS found: (M+H)⁺ = 620.3486.

5

Exempl 30

Ac-Val-Pro-(1R)-1-amino-3-(4-phenoxy)phenylpropylboronic
acid (+)-pinanediol ester

10 **(30a)** Following a procedure analogous to (17d), α -
aminoboronic ester **17c** (44 mg, 0.10 mmol) was coupled to
dipeptide **28b** (26 mg, 0.10 mmol) with EDCI, HOAt, and
sodium bicarbonate. The crude tripeptide was purified by
HPLC to afford the desired tripeptide boronic ester **30a**.
15 HRMS found: (M+H)⁺ = 644.3886.

Example 31

Ac-Val-Pro-(1R)-1-amino-3-(4-hydroxy)phenylpropylboronic
acid (+)-pinanediol ester

20

(31a) Following a procedure analogous to (17d), α -
aminoboronic ester **27c** (154 mg, 0.42 mmol) was coupled to
dipeptide **28b** (101 mg, 0.39 mmol) with EDCI, HOAt, and
sodium bicarbonate. The crude tripeptide was purified by
25 HPLC to afford the desired tripeptide boronic ester **31a** (56
mg, 25%). HRMS found: (M+H)⁺ = 568.3563.

Example 32

Ac-Val-Pro-(1R)-1-amino-3-(4-(4-methoxyphenoxy)phenyl)
30 propylboronic acid (+)-pinanediol ester

(32a) A solution of tripeptide boronic ester **31a** (20 mg,
0.035 mmol), 4-methoxyphenylboronic acid (32 mg, 0.21
mmol), copper(II) acetate (27 mg, 0.15 mmol), pyridine
35 (0.016 mL, 0.19 mmol), and morpholine (0.011 mL, 0.100) in
dichloromethane (1 mL) over molecular sieves (4Å, oven
dried) was stirred at rt overnight. The reaction mixture
was concentrated under reduced pressure and the residue was
purified by chromatography on silica gel (9:0.5
40 chloroform/methanol) followed by HPLC to afford the desired

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5 tripeptide boronic ester **32a**. HRMS found: (M+H)⁺ =
674.3947.

Example 33

Ac-Val-Pro-(1*R*)-1-amino-3-(4-(4-methylphenoxy)phenyl)
10 propylboronic acid (+)-pinanediol ester

(**33a**) A solution of tripeptide boronic ester **31a** (20 mg,
0.035 mmol), 4-methylphenylboronic acid (26 mg, 0.19 mmol),
copper(II) acetate (27 mg, 0.15 mmol), pyridine (0.016 mL,
15 0.19 mmol), and morpholine (0.011 mL, 0.100) in
dichloromethane (1 mL) over molecular sieves (4Å, oven
dried) was stirred at rt overnight. The reaction mixture
was concentrated under reduced pressure and the residue was
purified by chromatography on silica gel (9:0.5
20 chloroform/methanol) followed by HPLC to afford the desired
tripeptide boronic ester **33a**. HRMS found: (M+H)⁺ =
658.4051.

Example 34

25 (2-pyrazinecarbonyl)-Val-Val-Hyp(OBzl)-(1*R*)-1-amino-3-(4-
trifluoromethyl)phenylpropylboronic acid (+)-pinanediol
ester

(**34a**) Following a procedure analogous to (17d), α-
30 aminoboronic ester **14c** (36 mg, 0.086 mmol) was coupled to
thetripeptide (2-pyrazinecarbonyl)-Val-Val-Hyp(OBn)-OH
(prepared in a manner analogous to example 1) (30 mg, 0.057
mmol) with EDCI, HOAt, and sodium bicarbonate. The crude
material was purified by HPLC to afford the desired
35 tetrapeptide **34a** (23 mg, 45%). HRMS found: (M+H)⁺ =
889.4665.

Example 35

H-Asp-Glu-Val-Val-Pro-(1*R*)-1-aminohexylboronic acid (+)-
40 pinanediol ester

5 **(35a)** Using a procedure analogous to (3a), *n*-pentylmagnesium bromide (2M solution in ether, 13.3 ml, 26.6 mmol) was reacted with triisopropyl borate and (+)-pinanediol. Silica gel chromatography (9:1 hexane/ethyl acetate) afforded the desired boronic ester **35a** as a pale
10 yellow oil (3.33 g, 50%).

(35b) Using a procedure analogous to (2b), boronic ester **35a** (3.3 g, 13.2 mmol) was treated with *n*-butyllithium and dichloromethane in tetrahydrofuran to provide the desired
15 α -chloroboronic ester **35b** as a clear oil (2.5 g, 63%) after chromatography on silica gel.

(35c) Following a procedure analogous to (2c), α -chloroboronic ester **35b** (2.5 g, 8.37 mmol) was converted to the aminoboronic ester hydrochloride **35c** by treatment with
20 lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **35c** (0.57 g, 22%) was obtained as a colorless oil. MS found: $(M+H)^+ = 280.2$.

(35d) Following a procedure analogous to (2d), α -aminoboronic ester (**35c**) (18 mg, 0.056 mmol) was coupled to
25 pentapeptide **1h** (29 mg, 0.038 mmol) with PyAOP and DIEA and purified by HPLC to afford the desired hexapeptide **35d** (9 mg, 23%). MS found: $(M+H)^+ = 1031.7$.

(35e) Following a procedure analogous to (2e), the hexapeptide **35d** (4 mg, 0.004 mmol) was deprotected with TFA
30 and triisopropylsilane and purified by HPLC to afford the desired hexapeptide **35e** as a white solid. HRMS found:
 $(M+H)^+ = 819.5$.

Example 36

35 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-5-methylhexylboronic acid (+)-pinanediol ester

5 **(36a)** Using a procedure analogous to (3a), 4-methyl-3-pentenylmagnesium bromide (18.4 mmol) was reacted with triisopropyl borate and (+)-pinanediol. Silica gel chromatography (9:1 hexane/ethyl acetate) afforded the desired boronic ester **36a** as a pale yellow oil (2.4 g, 10 50%).

(36b) Using a procedure analogous to (2b), boronic ester **36a** (0.6 g, 13.2 mmol) was treated with *n*-butyllithium and dichloromethane in tetrahydrofuran to provide the desired 15 α -chloroboronic ester **36b** as a clear oil (0.58 g, 82%) after chromatography on silica gel.

(36c) Following a procedure analogous to (2c), α -chloroboronic ester **36b** (252 mg, 0.81 mmol) was converted 20 to the aminoboronic ester hydrochloride **36c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **36c** (0.26 g, 99%) was obtained as a colorless solid. HRMS found: $(M+H)^+ = 292.2$.

(36d) Following a procedure analogous to (2d), α -aminoboronic ester (**36c**) (80 mg, 0.244 mmol) was coupled to 25 pentapeptide **1h** (125 mg, 0.163 mmol) with PyAOP and DIEA and purified by HPLC to afford the desired hexapeptide **36d** (135 mg, 79%). HRMS found: $(M+H)^+ = 1043.6$.

(36e) A solution of hexapeptide **36d** (52 mg, 0.050 mmol) in 30 methanol (2 mL) containing hydrochloric acid (1 drop) was hydrogenated (1 atm) over 20% palladium on carbon at room temperature overnight. The solution was filtered to yield the desired hexapeptide (50 mg, 96%). MS found: $(M+H)^+ = 1045.9$.

35 **(36f)** Following a procedure analogous to (2e), the hexapeptide **36e** (50 mg, 0.048 mmol) was deprotected with TFA and triisopropylsilane and purified by HPLC to afford

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5 the desired hexapeptide **36** as a white solid (3 mg, 7.5%).
MS found: (M+H)⁺ = 833.5.

Example 37

10 H-Asp-Glu-Val-Val-Pro-(1R)-1-aminoheptylboronic acid (+)-
pinanediol ester

(**37a**) Using a procedure analogous to (3a), *n*-hexylmagnesium bromide (2M solution in ether, 32 ml, 64 mmol) was reacted with triisopropyl borate and (+)-pinanediol. Silica gel
15 chromatography (9:1 hexane/ethyl acetate) afforded the desired boronic ester **37a** as a pale yellow oil (10.6 g, 75%).

(**37b**) Using a procedure analogous to (2b), boronic ester
20 **37a** (10.6 g, 40.1 mmol) was treated with *n*-butyllithium and dichloromethane in tetrahydrofuran to provide the desired α -chloroboronic ester **37b** as a clear oil (12 g, 95%) after chromatography on silica gel.

(**37c**) Following a procedure analogous to (2c), α -
25 chloroboronic ester **37b** (12 g, 38 mmol) was converted to the aminoboronic ester hydrochloride **37c** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product **37c** was obtained as a colorless oil.

30 (**37d**) Following a procedure analogous to (2d), α -aminoboronic ester (**37c**) (86 mg, 0.26 mmol) was coupled to pentapeptide **1h** (50 mg, 0.065 mmol) with PyAOP and DIEA and purified by HPLC to afford the desired hexapeptide **37d** (7 mg, 10%).

35 (**37e**) Following a procedure analogous to (2e), the hexapeptide **37d** (7 mg, 0.007 mmol) was deprotected with TFA and triisopropylsilane and purified by HPLC to afford the

5 desired hexapeptide **37e** as a white solid. MS found: $(M+H)^+$
= 833.6.

Example 38

10 H-Asp-Glu-Val-Val-Pro-(1*R*)-1-amino-4-cyclobutylbutylboronic
acid (+)-pinanediol ester

(**38a**) A solution of cyclobutylbromide (5 g, 37 mmol) in ether (15 mL) was added slowly dropwise to a suspension of magnesium (1.8 g, 74 mmol) and iodine (1 granule) in ether
15 (15 mL). The reaction mixture was then refluxed for 2 h. The solution was cooled to RT and then added slowly dropwise to a solution of allyl bromide (3.2 mL, 37 mmol) in ether (10 mL) at 0°C. The reaction mixture was allowed to warm to RT and stir overnight. The solution was diluted
20 with ether and washed with saturated ammonium chloride solution. The solvent was removed by distillation at atmospheric pressure, and the desired olefin **38a** was isolated by vacuum distillation as a colorless oil (1.65 g, 46%). ^{13}C NMR δ (ppm) 137.0, 114.7, 41.0, 35.2, 27.8, 18.4.

25 (**38b**) Using a procedure analogous to (8a), olefin **38a** (1.6 g, 16.5 mmol) was reacted with catecholborane and then (+)-pinanediol. After chromatography on silica gel (10:1 hexane/ethyl acetate), the desired boronic ester (**38b**) was
30 isolated as a colorless oil (3.2 g, 70%).

(**38c**) Using a procedure analogous to (2b), boronic ester **38b** (1 g, 3.6 mmol) was treated with *n*-butyllithium and dichloromethane in tetrahydrofuran to provide the desired α -chloroboronic ester **38c** as a clear oil (1.05 g, 80%)
35 after chromatography on silica gel.

(**38d**) Following a procedure analogous to (2c), α -chloroboronic ester **38c** (0.5 g, 1.54 mmol) was converted to the aminoboronic ester hydrochloride **38d** by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen

5 chloride. The desired product **38d** (0.5 g, 94%) was obtained as a colorless oil. MS found: $(M+H)^+ = 306.3$.

(**38e**) Following a procedure analogous to (2d), α -aminoboronic ester (**38d**) (20 mg, 0.058 mmol) was coupled to pentapeptide **1h** (30 mg, 0.039 mmol) with PyAOP and DIEA and
10 purified by HPLC to afford the desired hexapeptide **38e**. MS found: $(M+H)^+ = 1057.9$.

(**38f**) Following a procedure analogous to (2e), the hexapeptide **38e** was deprotected with TFA and triisopropylsilane and purified by HPLC to afford the
15 desired hexapeptide **38f** as a white solid. MS found: $(M+H)^+ = 845.1$.

Example 39

H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-5-ethylheptylboronic
20 acid (+)-pinanediol ester

(**39a**) Using a procedure analogous to (38a) 3-bromopropane was reacted with magnesium and then allyl bromide. The desired olefin **39a** was isolated by vacuum distillation as a
25 colorless oil (0.84 g, 14%).

(**39b**) Using a procedure analogous to (8a), olefin **39a** (0.84 g, 7.5 mmol) was reacted with catecholborane and then (+)-pinanediol. After chromatography on silica gel (10:1
30 hexane/ethyl acetate), the desired boronic ester (**39b**) was isolated as a colorless oil (0.48 g, 87%).

(**39c**) Using a procedure analogous to (2b), boronic ester **39b** (0.48 g, 1.6 mmol) was treated with *n*-butyllithium and
35 dichloromethane in tetrahydrofuran to provide the desired α -chloroboronic ester **39c** as a clear oil (0.186 g, 66%) after chromatography on silica gel.

5 (39d) Following a procedure analogous to (2c), α -chloroboronic ester 39c (0.5 g, 1.54 mmol) was converted to the aminoboronic ester hydrochloride 39d by treatment with lithium bis(trimethylsilyl)amide followed by hydrogen chloride. The desired product 39d (0.15 g, 77%) was
 10 obtained as a colorless oil.

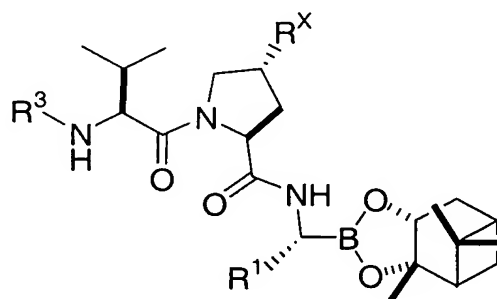
(39e) Following a procedure analogous to (2d), α -aminoboronic ester (39d) (21 mg, 0.058 mmol) was coupled to pentapeptide 1h (30 mg, 0.039 mmol) with PyAOP and DIEA and purified by HPLC to afford the desired hexapeptide 39e. MS
 15 found: (M+H)⁺ = 1073.9.

(39f) Following a procedure analogous to (2e), the hexapeptide 39e was deprotected with TFA and triisopropylsilane and purified by HPLC to afford the
 20 desired hexapeptide 39f as a white solid. MS found: (M+H)⁺ = 861.6.

Table 1 provides representative Examples of the compounds of Formula (I) of the present invention.

25

TABLE 1



Ex.	R ¹	R ³	R ^X	MS (M+H) ⁺
2	phenyl	H-Asp-Glu-Val-	H	825.5
3	2-phenylethyl	H-Asp-Glu-Val-	H	853.5
4	3-phenylpropyl	H-Asp-Glu-Val-	H	867.5
5	4-phenylbutyl	H-Asp-Glu-Val-	H	881.5
7	2-(2-naphthyl)ethyl	H-Asp-Glu-Val-	H	903.5

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8	2-(2-methylphenyl)ethyl	H-Asp-Glu-Val-	H	867.5
9	2-(3-methylphenyl)ethyl	H-Asp-Glu-Val-	H	867.5
10	2-(4-methylphenyl)ethyl	H-Asp-Glu-Val-	H	867.5
11	2-(1,1'-biphenyl)-4-ylethyl	H-Asp-Glu-Val-	H	929.5
12	2-(2,5-dimethylphenyl)ethyl	H-Asp-Glu-Val-	H	881.5
13	2-(2,4-dimethylphenyl)ethyl	H-Asp-Glu-Val-	H	881.5
14	2-(4-trifluoromethylphenyl)ethyl	H-Asp-Glu-Val-	H	921.5
15	2-(3-trifluoromethylphenyl)ethyl	H-Asp-Glu-Val-	H	921.5
16	2-(4-fluorophenyl)ethyl	H-Asp-Glu-Val-	H	871.5
17	2-(4-phenoxyphenyl)ethyl	H-Asp-Glu-Val-	H	945.5
18	2-(4-isopropylphenyl)ethyl	H-Asp-Glu-Val-	H	895.5
19	2-(4-cyclohexylphenyl)ethyl	H-Asp-Glu-Val-	H	935.6
20	2-(4-tert-butylphenyl)ethyl	H-Asp-Glu-Val-	H	909.6
21	2-(4-methoxyphenyl)ethyl	H-Asp-Glu-Val-	H	883.5
22	2-(4-chlorophenyl)ethyl	H-Asp-Glu-Val-	H	887.4
23	2-(4-bromophenyl)ethyl	H-Asp-Glu-Val-	H	931.4
24	2-(2-fluorophenyl)ethyl	H-Asp-Glu-Val-	H	871.5
25	2-(3-fluorophenyl)ethyl	H-Asp-Glu-Val-	H	869.5
26	2-(2,6-difluorophenyl)ethyl	H-Asp-Glu-Val-	H	889.5
27	2-(4-hydroxyphenyl)ethyl	H-Asp-Glu-Val-	H	869.5
28	2-phenylethyl	Ac-	H	552.4
29	2-(4-trifluoromethylphenyl)ethyl	Ac-	H	620.3
30	2-(4-phenoxyphenyl)ethyl	Ac-	H	644.4
31	2-(4-hydroxyphenyl)ethyl	Ac-	H	568.4
32	2-(4-(4-methoxyphenoxy)phenyl)ethyl	Ac-	H	674.4
33	2-(4-(4-methylphenoxy)phenyl)ethyl	Ac-	H	658.4
34	2-(4-trifluoromethylphenyl)ethyl	(2-pyrazine-carbonyl)-Val-	OBzl	889.5
35	pentyl	H-Asp-Glu-Val-	H	819.5
36	4-methylpentyl	H-Asp-Glu-Val-	H	833.5
37	hexyl	H-Asp-Glu-Val-	H	833.6
38	3-cyclobutylpropyl	H-Asp-Glu-Val-	H	845.1
39	4-ethylhexyl	H-Asp-Glu-Val-	H	861.6

5

UTILITY

The compounds of Formula (I) are expected to inhibit the activity of Hepatitis C Virus NS3 protease. The NS3 protease inhibition is demonstrated using assays for NS3 protease activity, for example, using the assay described below for assaying inhibitors of NS3 protease. Thus, the compounds of Formula (I) are potentially useful in the cure and prevention of HCV infections. Additionally, compounds of the present invention demonstrate unexpected inhibitory selectivity of HCV NS3 protease over elastase inhibition. Additionally, it is expected that compounds of the present invention may show unexpected inhibitory selectivity of HCV NS3 protease over chymotrypsin inhibition.

Biological ActivityExpression and Purification of NS3 Protease

The plasmid cf1SODp600, containing the complete coding region of HCV NS3 protease, genotype 1a, was obtained from ATCC (database accession: DNA Seq. Acc. M62321, originally deposited by Chiron Corporation). PCR primers were designed that allow amplification of the DNA fragment encoding the NS3 protease catalytic domain (amino acids 1 to 192) as well as its two N-terminal fusions, a 5 amino acid leader sequence MGAQH (serving as a expression tag) and a 15 amino acid His tag MRGSHHHHHMGAQH. The NS3 protease constructs were cloned in the bacterial expression vector under the control of the T7 promoter and transformed in *E. coli* BL 21 (DE3) cells. Expression of the NS3 protease was obtained by addition of 1 mM IPTG and cells were grown for an additional 3 h at 25°C. The NS3 protease constructs have several fold difference in expression level, but exhibit the same level of solubility and enzyme specific activity. A typical 10 L fermentation yielded approximately 200 g of wet cell paste. The cell paste was stored at -80°C. The NS3 protease was purified based on published procedures (Steinkuhler C. et al. *Journal of Virology* 70, 6694-6700, 1996 and Steinkuhler C. et al. *Journal of Biological Chemistry* 271, 6367-6373, 1996.) with some modifications. Briefly, the cells were resuspended in lysis buffer (10 ml/g) containing PBS buffer (20 mM sodium phosphate, pH 7.4, 140 mM NaCl), 50% glycerol, 10 mM DTT, 2% CHAPS and 1mM PMSF. Cell lysis was performed with use of microfluidizer. After homogenizing, DNase was added to a final concentration 70 U/ml and cell lysate was incubated at 4°C for 20 min. After centrifugation at 18,000 rpm for 30 min at 4°C supernatant was applied on SP Sepharose column (Pharmacia), previously equilibrated at a flow rate 3 ml/min in buffer A (PBS buffer, 10% glycerol, 3 mM DTT). The column was extensively washed with buffer A and the

5 protease was eluted by applying 25 column volumes of a
linear 0.14 - 1.0 M NaCl gradient. NS3 containing fractions
were pooled and concentrated on an Amicon stirred
ultrafiltration cell using a YM-10 membrane. The enzyme was
further purified on 26/60 Superdex 75 column (Pharmacia),
10 equilibrated in buffer A. The sample was loaded at a flow
rate 1 ml/min, the column was then washed with a buffer A
at a flow rate 2 ml/min. Finally, the NS3 protease
containing fractions were applied on Mono S 10/10 column
(Pharmacia) equilibrated in 50 mM Tris.HCl buffer, pH 7.5,
15 10% glycerol and 1 mM DTT and operating at flow rate 2
ml/min. Enzyme was eluted by applying 20 column volumes of
a linear 0.1 - 0.5 M NaCl gradient. Based on SDS-PAGE
analysis as well as HPLC analysis and active site
titration, the purity of the HCV NS3 1a protease was
20 greater than 95%. The enzyme was stored at -70°C and
diluted just prior to use.

NS3 Protease Enzyme Assays

Concentrations of protease were determined in the absence
25 of NS4a by using the peptide ester substrate Ac-
DED(Edans)EEAbuψ[COO]ASK(Dabcyl)-NH₂ (Taliani et al. *Anal.*
Biochem. 240, 60-67, 1996.) and the inhibitor, H-Asp-Glu-
Val-Val-Pro-boroAlg-OH and by using tight binding reaction
conditions (Bieth, *Methods Enzymol.* 248, 59-85, 1995). Best
30 data was obtained for an enzyme level of 50 nM.

Alternately, protease (63 µg/ml) was allowed to react with
3 µM NS4a, 0.10 mM Ac-Glu-Glu-Ala-Cys-pNA, and varying
level of H-Asp-Glu-Val-Val-Pro-boroAlg-OH (0-6 µM).
Concentrations of protease were determined from linear
35 plots of Activity vs. [inhibitor]. Molar concentrations of
proteases were determined from the x-intercept.

K_m values were determined measuring the rate of hydrolysis
of the ester substrate over a range of concentrations from
5.0 to 100 µM in the presence of 3 µM KKNS4a
40 (KKGSVVIVGRIVLSGKPAIIPKK). Assay were run at 25°C, by

5 incubating ~1 nM enzyme with NS4a for 5 min in 148 μ l of
buffer (50 mM Tris buffer, pH 7.0, 50% glycerol, 2% Chaps,
and 5.0 mM DTT. Substrate (2.0 μ l) in buffer was added and
the reaction was allowed to proceed for 15 min. Reactions
were quenched by adding 3.0 μ L of 10% TFA, and the levels
10 of hydrolysis were determined by HPLC. Aliquots (50 μ L)
were injected on the HPLC and linear gradients from 90%
water, 10% acetonitrile and 0.1 % TFA to 10% water, 90%
acetonitrile and 0.1% TFA were run at a flow rate of 1.0
mL/min over a period of 30 min. HPLCs were run on a HP1090
15 using a Rainin 4.6 x 250 mm C18 column (cat # 83-201-C)
fluorescent detection using 350 and 500 nm as excitation
and emission wavelengths, respectively. Levels of
hydrolysis were determined by measuring the area of the
fluorescent peak at 5.3 min. 100% hydrolysis of a 5.0 μ M
20 sample gave an area of 7.95 ± 0.38 fluorescence units.).
Kinetic constants were determined from the iterative fit of
the Michaelis equation to the data. Results are consistent
with data from Liveweaver Burk fits and data collected for
the 12.8 min peak measured at 520 nm.

25 Enzyme activity was also measured by measuring the
increase in fluorescence with time by exciting at 355 nm
and measuring emission at 495 nm using a Perkin Elmer LS 50
spectrometer. A substrate level of 5.0 μ M was used for all
fluorogenic assays run on the spectrometer.

30

NS3 Protease Inhibitor Evaluation In vitro

Inhibitor effectiveness was determined by measuring enzyme
activity both in the presence and absence of inhibitor.
Velocities were fit to the equation for competitive
35 inhibition for individual reactions of inhibitors with the
enzyme using

$$v_i / v_o = [K_m (1 + I/K_i) + S] / [K_m + S].$$

The ratio v_i / v_o is equal to the ratio of the Michaelis
equations for velocities measured in the presence (v_i) and

5 absence (v_0) of inhibitor. Values of v_i / v_0 were measured over a range of inhibitor concentrations with the aid of an Excel™ Spreadsheet. Reported K_i values are the average of 3-5 separate determinations. Under the conditions of this assay, the IC_{50} and K_i 's are comparable measures of
10 inhibitor effectiveness.

Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq 50 \mu M$. Preferred compounds of the present invention have K_i 's of $\leq 1 \mu M$. More preferred compounds of the present invention have K_i 's of
15 $\leq 0.1 \mu M$. Even more preferred compounds of the present invention have K_i 's of $\leq 0.01 \mu M$. Still more preferred compounds of the present invention have K_i 's of $\leq 0.001 \mu M$.

Using the methodology described above, compounds of the present invention were found to exhibit a K_i of $\leq 50 \mu M$,
20 thereby confirming the utility of the compounds of the present invention as effective HCV NS3 protease inhibitors.

NS3 Protease Inhibitor Evaluation of in Cell Assay.

The following method was devised to assess inhibitory
25 action of test compounds on the HCV NS3 protease in cultured cells. Because it is not presently possible to efficiently infect cells with hepatitis C virus, an assay was developed based on co-expression in transfected cell lines of two plasmids, one is able to direct synthesis of
30 the NS3 protease and the other to provide a polypeptide analogous to a part of the HCV non-structural protein containing a single known peptide sequence highly susceptible to cleavage by the protease. When installed in cultured cells by one of a variety of standard methods, the
35 substrate plasmid produces a stable polypeptide of approximately 50KD, but when the plasmid coding for the viral protease is co-expressed, the enzymatic action of the protease hydrolyzes the substrate at a unique sequence between a cysteine and a serine pair, yielding products
40 which can be detected by antibody-based technology, eg, a

5 western blot. Quantitation of the amounts of precursor and
products can be done by scanning film auto-radiograms of
the blots or direct luminescence-based emissions from the
blots in a commercial scanning device. The general
organization of the two plasmids is disclosed in a PCT
10 application PCT/US00/18655. The disclosure of which is
hereby incorporated by reference. The coding sequences for
the NS3 protease and the substrate were taken from genotype
1a of HCV, but other genotypes, eg 2a, may be substituted
with similar results.

15 The DNA plasmids are introduced into cultured cells
using electroporation, liposomes or other means. Synthesis
of the protease and the substrate begin shortly after
introduction and may be detected within a few hours by
immunological means. Therefore, test compounds are added at
20 desired concentrations to the cells within a few minutes
after introducing the plasmids. The cells are then placed
in a standard CO₂ incubator at 37°C, in tissue culture
medium eg Dulbecco-modified MEM containing 10% bovine
serum. After 6-48 hours, the cells are collected by
25 physically scraping them from plastic dishes in which they
have been growing, centrifuging them and then lysing about
10⁶ of the concentrated cells in a minimal volume of
buffered detergent, eg 20 µL of 1% sodium dodecyl sulfate
in 0.10 M Tris-HCl, pH 6.5, containing 1% mercaptaethanol
30 and 7% glycerol. The samples are then loaded onto a
standard SDS polyacrylamide gel, the polypeptides separated
by electrophoresis, and the gel contents then
electroblotted onto nitrocellulose or other suitable paper
support, and the substrate and products detected by
35 decoration with specific antibodies.

Inhibitory Selectivity

In addition to the inhibitory activity against
HCV NS3 protease exhibited by the compounds of Formula (1),
40 Applicants have discovered unexpected benefit of
selectivity over inhibition of elastase and/or chymotrypsin

5 proteases. Most HCV NS3 protease inhibitors reported do
not show selectivity over elastase. Selectivity of HCV NS3
over elastase can be calculated by dividing IC_{50} (elastase)
over IC_{50} (HCV NS3). Similarly, selectivity of HCV NS3
over chymotrypsin can be calculated by dividing IC_{50}
10 (chymotrypsin) over IC_{50} (HCV NS3).

Inhibition Evaluation of Elastase Protease

Human neutrophil elastase was obtained from ART
Biochemicals, Athens, Georgia. Stock solutions of
15 lyophilized enzyme (1 mg/ml) were prepared in PBS buffer
containing 10% glycerol and stored at -20°C . Human
neutrophil elastase was assayed with the Meo-Suc-Ala-Ala-
Pro-Val-p-nitroanilide (Sigma) as a substrate (C. Kettner
and A. Shenvi, 1984). The hydrolysis of substrate was
20 monitored at 405 nm on a Hewlett-Packard spectrophotometer.
Kinetic parameters were determined in PBS buffer at room
temperature with concentration of DMSO did not exceed 2%.

Representative compounds of the present invention have
been tested using the assay discussed herein for
25 selectivity over elastase. Table 2 shows unexpected result
of inhibitory selectivity of HCV NS3 protease over elastase
exhibited by the compounds of the instant invention. In
Table 2, NA indicates that inhibition of elastase of the
compound was not tested.

30

TABLE 2

Ex.	Selectivity of HCV NS3 vs. elastase
2	NA
3	>10
4	NA
5	9
7	NA
8	NA
9	>10
10	>10
11	>10
12	NA
13	NA
14	>10
15	NA

132

16	>10
17	>10
18	>10
19	>10
20	>10
21	>10
22	>10
23	>10
24	NA
25	NA
26	NA
27	>10
28	NA
29	NA
30	NA
31	NA
32	NA
33	NA
34	7
35	NA
36	>10
37	NA
38	NA
39	NA

5

Inhibition Evaluation of Chymotrypsin Protease

Human pancreatic chymotrypsin was obtained from Calbiochem, San Diego, California. Stock solutions of lyophilized enzyme (20 uM) were prepared in 1 mM hydrochloric acid and stored at -20°C. Human pancreatic chymotrypsin was assayed with the Suc-Ala-Ala-Pro-Phe-p-nitroanilide (Calbiochem cathepsin G substrate #219407) as a substrate. The hydrolysis of substrate was monitored at 405 nm on a Titertek Multiscan MCC/340 plate reader. Kinetic parameters were determined in 0.1 M Tris, pH 7.8, 10 mM CaCl₂ buffer at room temperature with a concentration of DMSO that did not exceed 2%.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

25

DOSAGE AND FORMULATION

The HCV protease inhibitor compounds of this invention can be administered as treatment for the control or prevention of hepatitis C virus infections by any means that produces contact of the active agent with the agent's site of action, i.e., the NS3 protease, in the body of a mammal. It can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as an individual therapeutic agent or in a combination of therapeutic agents. It can be administered alone, but preferably is administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. By way of general guidance, a daily dosage of active ingredient can be expected to be about 0.001 to about 1000 milligrams per kilogram of body weight, with the preferred dose being about 0.01 to about 100 mg/kg; with the more preferred dose being about 0.1 to about 30 mg/kg. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

5 Dosage forms of compositions suitable for
administration contain from about 1 mg to about 100 mg of
active ingredient per unit. In these pharmaceutical
compositions the active ingredient will ordinarily be
present in an amount of about 0.5-95% by weight based on
10 the total weight of the composition. The active ingredient
can be administered orally in solid dosage forms, such as
capsules, tablets and powders, or in liquid dosage forms,
such as elixirs, syrups and suspensions. It can also be
administered parenterally, in sterile liquid dosage forms.
15 Gelatin capsules contain the active ingredient and
powdered carriers, such as lactose, starch, cellulose
derivatives, magnesium stearate, stearic acid, and the
like. Similar diluents can be used to make compressed
tablets. Both tablets and capsules can be manufactured as
20 sustained release products to provide for continuous
release of medication over a period of hours. Compressed
tablets can be sugar coated or film coated to mask any
unpleasant taste and protect the tablet from the
atmosphere, or enteric coated for selective disintegration
25 in the gastrointestinal tract. Liquid dosage forms for
oral administration can contain coloring and flavoring to
increase patient acceptance.

In general, water, a suitable oil, saline, aqueous
dextrose (glucose), and related sugar solutions and glycols
30 such as propylene glycol or polyethylene glycols are
suitable carriers for parenteral solutions. Solutions for
parenteral administration preferably contain a water
soluble salt of the active ingredient, suitable stabilizing
agents, and if necessary, buffer substances. Antioxidizing
35 agents such as sodium bisulfite, sodium sulfite, or
ascorbic acid, either alone or combined, are suitable
stabilizing agents. Also used are citric acid and its
salts, and sodium EDTA. In addition, parenteral solutions
can contain preservatives, such as benzalkonium chloride,
40 methyl- or propyl-paraben and chlorobutanol. Suitable
pharmaceutical carriers are described in *Remington's*

5 *Pharmaceutical Sciences, supra*, a standard reference text
in this field.

Useful pharmaceutical dosage-forms for administration
of the compounds of this invention can be illustrated as
follows:

10

Capsules

A large number of unit capsules can be prepared by
filling standard two-piece hard gelatin capsules each with
100 mg of powdered active ingredient, 150 mg of lactose, 50
15 mg of cellulose, and 6 mg magnesium stearic.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil
20 such as soybean oil, cottonseed oil or olive oil can be
prepared and injected by means of a positive displacement
pump into gelatin to form soft gelatin capsules containing
100 mg of the active ingredient. The capsules should then
be washed and dried.

25

Tablets

A large number of tablets can be prepared by
conventional procedures so that the dosage unit is 100 mg
of active ingredient, 0.2 mg of colloidal silicon dioxide,
30 5 milligrams of magnesium stearate, 275 mg of
microcrystalline cellulose, 11 mg of starch and 98.8 mg of
lactose. Appropriate coatings may be applied to increase
palatability or delay absorption.

35 Suspension

An aqueous suspension can be prepared for oral
administration so that each 5 ml contain 25 mg of finely
divided active ingredient, 200 mg of sodium carboxymethyl
cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol
40 solution, U.S.P., and 0.025 mg of vanillin.

5 Injectable

A parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.